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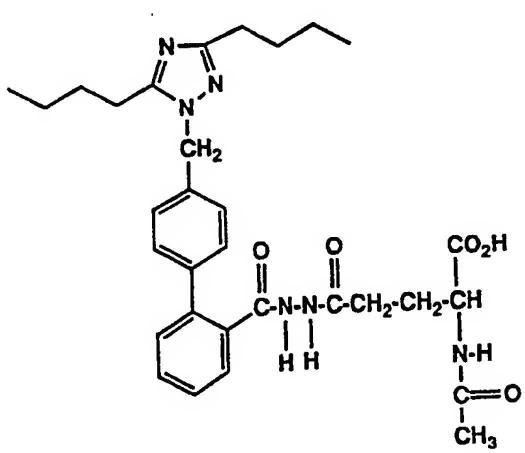

(I)

(57) Abstract

Renal-selective compounds are described which, in one embodiment, are prodrugs preferentially converted in the kidney to compounds capable of blocking angiotensin II (AII) receptors. These prodrugs are conjugates formed from two components, namely, a first component provided by an AII antagonist compound and a second component which is capable of being cleaved from the first component when both components are chemically linked within the conjugate. The two components are chemically linked by a bond which is cleaved selectively in the kidney, for example, by an enzyme. The liberated AII antagonist compound is then available to block AII receptors within the kidney. Conjugates of particular interest are glutamyl derivatives of biphenylmethyl 1H-substituted-1,2,4-triazole compounds, of which N-acetylglutamic acid, 5-[[4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]]carbonylhydrazide is an example.

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RENAL-SELECTIVE BIPHENYLALKYL 1H-SUBSTITUTED-1,2,4-TRIAZOLE ANGIOTENSIN II ANTAGONISTS FOR TREATMENT OF HYPERTENSION

Related Application

This a continuation-in-part of U.S. Application Ser. No. 07/574,314 filed August 28, 1990.

Field of the Invention

This invention is in the field of cardiovascular therapeutics and relates to a class of compounds useful in control of hypertension. Of particular interest is a class of prodrugs of angiotensin II antagonists which, when selectively hydrolyzed in the kidney, provide hypertension control.

Background of the Invention

The renin-angiotensin system is one of the hormonal mechanisms involved in regulation of pressure/volume homeostasis and in expression of hypertension. Activation of the renin-angiotensin cascade begins with renin secretion from the juxtaglomerular apparatus of the kidney and culminates in the formation of angiotensin II, an octapeptide which is the primary active species of this system. Angiotensin II is a potent vasoconstrictor agent and also produces other physiological effects such as promoting aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity, increasing vasopressin secretion, causing positive cardiac inotropic effect and modulating other hormonal systems.

Previous studies have shown that antagonizing angiotensin II at its receptors is a viable approach to inhibit the renin-angiotensin system, given the pivotal

role of this octapeptide which mediates the actions of the renin-angiotensin system through interaction with various tissue receptors. There are several known angiotensin II antagonists, most of which are peptidic in nature. Such peptidic compounds are of limited use due to their lack of oral bioavailability or their short duration of action. Also, commercially-available peptidic angiotensin II antagonists (e.g., Saralasin) have a significant residual agonist activity which further limit their therapeutic application.

Non-peptidic compounds with angiotensin II antagonist properties are known. For example, the sodium salt of 2-n-butyl-4-chloro-1-(2-chlorobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [P. C. Wong et al, J. Pharmacol. Exp. Ther., 247(1), 1-7 (1988)]. Also, the sodium salt of 2-butyl-4-choloro-1-(2-nitrobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [A. T. Chiu et al, European J. Pharmacol., 157, 3121 (1988)]. A family of 1-benzylimidazole-5-acetate derivatives has been shown to have competitive angiotensin II antagonist properties [A. T. Chiu et al, J. Pharmacol. Exp. Ther., 250(3), 867-874 (1989)]. U.S. Patent No. 4,816,463 to Blankey et al describes a family of 4,5,6,7-tetrahydro-1H-imidazo(4,5-c)-tetrahydro-pyridine derivatives useful as antihypertensives, some of which are reported to antagonize the binding of labelled angiotensin II to rat adrenal receptor preparation and thus cause a significant decrease in mean arterial blood pressure in conscious hypertensive rats. EP No. 253,310, published 20 January 1988, describes a series of aralkyl imidazole compounds, including in particular a family of biphenylmethyl substituted imidazoles, as antagonists to

the angiotensin II receptor. EP No. 323,841, published 12 July 1989, describes four classes of angiotensin II antagonists, namely, biphenylmethylpyrroles, biphenylmethylpyrazoles, biphenylmethyl-1,2,3-triazoles and biphenylmethyl 4-substituted-4H-1,2,4-triazoles, including the compound 3,5-dibutyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-4H-1,2,4-triazole. U.S. Patent No. 4,880,804 to Carini et al describes a family of biphenylmethylbenzimidazole compounds as angiotensin II receptor blockers for use in treatment of hypertension and congestive heart failure.

One disadvantage of these angiotensin II antagonist compounds is that the desired hypertension-reducing effect may be offset by hypotension-induced compensatory stimulation of the renin-angiotensin system or stimulation of the sympathetic nervous system, either of which may result in promotion of sodium and water retention. Also, some angiotensin II antagonists may have toxicological effects systemically which preclude their use at doses necessary to be effective in reducing blood pressure.

To avoid such systemic side effects, drugs may be targetted to the kidney by creating a conjugate compound that would be a renal-specific prodrug containing the targetted drug modified with a chemical carrier moiety. Cleavage of the drug from the carrier moiety by enzymes predominantly localized in the kidney releases the drug in the kidney. Gamma glutamyl transpeptidase and acylase are examples of such cleaving enzymes found in the kidney which have been used to cleave a targetted drug from its prodrug carrier within the kidney.

Renal targetted prodrugs are known for delivery of a drug selectively to the kidney. For example, the compound L-γ-glutamyl amide of dopamine when administered to dogs was reported to generate dopamine _in vivo_ by

specific enzymatic cleavage by γ-glutamyl transpeptidase [J. J. Kyncl et al, Adv. Biosc., 20, 369-380 (1979)]. In another study, γ-glutamyl and N-acyl-γ-glutamyl derivatives of the anti-bacterial compound sulfamethoxazole were shown to deliver relatively high concentrations of sulfamethoxazole to the kidney which involved enzymatic cleavage of the prodrug by acylamino acid deacylase and γ-glutamyl transpeptidase [M. Orlowski et al, J. Pharmacol. Exp.Ther., 212, 167-172 (1980)]. The N-γ-glutamyl derivatives of 2-, 3-, or 4-aminophenol and p-fluoro-L-phenylalanine have been found to be readily solvolyzed in vitro by γ-glutamyl transpeptidase [S.D.J. Magnan et al, J. Med. Chem., 25, 1018-1021 (1982)]. The hydralazine-like vasodilator 2-hydrazino-5-γ-butylpyridine (which stimulates guanylate cyclase activity) when substituted with the N-acetyl-γ-glutamyl residue resulted in a prodrug which provided selective renal vasodilation [K. G. Hofbauer et al, J. Pharmacol. Exp. Ther., 212, 838-844 (1985)]. The dopamine prodrug γ-L-glutamyl-L-dopa ("gludopa") has been shown to be relatively specific for the kidney and to increase renal blood flow, glomerular filtration and urinary sodium excretion in normal subjects [D. P. Worth et al, Clin. Sci., 69, 207-214 (1985)]. In another study, gludopa was reported to be an effective renal dopamine prodrug whose activity can be blocked by the dopa-decarboxylase inhibitor carbidopa [R. F. Jeffrey et al, Br. J. Clin. Pharmac., 25, 195-201 (1988)]. A class of 4-ureido derivatives of isoquinolin-3-ol has been investigated for renal specific effects, such as increases in renal vasodilation and renal blood flow [R. M. Kanojia et al, J. Med. Chem., 32, 990-997 (1989)].

BRIEF DESCRIPTION OF THE DRAWING FIGURES

Fig. 1 is a graph showing reduction in mean arterial pressure by intravenous administration of a

conjugate of the invention to rats over a period of four days.

Fig. 2 is a graph showing angiotensin II pressor response by intravenous administration of a conjugate of the invention to rats over a period of four days.

Fig. 3 is a graph showing change in heart rate upon intravenous administration of a conjugate of the invention to rats over a period of four days.

Description of the Invention

Treatment of circulatory disorders, which include cardiovascular disorders, such as chronic hypertension, sodium-retaining disorders, congestive heart failure, cirrhosis and nephrosis, may be accomplished by administering to a susceptible or afflicted subject a therapeutically-effective amount of a renal-selective prodrug capable of causing blood-pressure reducing effects by selective action in the kidney. An advantage of such renal-selective prodrug therapy resides in reduction or avoidance of adverse side effects associated with systemically-acting drugs.

Advantages of a renal-selective antihypertensive compound are several. First, the renal-selective compound is targetted at those pathophysiological mechanisms which occur primarily in the kidney. Second, the regulation of other organ systems is unaffected; thus, normal physiological regulation of other organ systems is maintained. Third, fewer side-effects may be anticipated, since the compound remains inactive until cleaved in the kidneys. Similarly, fewer negative drug-drug interactions may be anticipated. Finally, since a renal-selective accumulation of active compound may occur, which is not dependent on plasma levels of the parent compound, lower

doses of the renal-selective compound compared to active parent compound may be used.

A renal-selective prodrug is provided by a conjugate comprising a residue of an angiotensin II antagonist compound, which conjugate is renal selective. The conjugate will typically comprise a first component and a second component connected together by a cleavable or hydrolyzable bond. The term "renal-selective", as used to characterize a conjugate of the invention, embraces any of the following four pharmacological events: (1) the conjugate is selectively taken up by the kidney and is selectively cleaved in the kidney; (2) the conjugate is not taken up selectively by the kidney, but is selectively cleaved in the kidney; (3) the conjugate is selectively taken up by the kidney and then cleaved in the kidney; or (4) where the conjugate itself is active as an angiotensin II antagonist, the conjugate is selectively taken up by the kidney without cleavage of the hydrolyzable bond.

The first component of a conjugate of the invention is a residue derived from an antagonist compound capable of inhibiting angiotensin II (AII) receptors, especially those AII receptors located in the kidney. The second residue is capable of being cleaved from the first residue preferential-ly. Cleaving of the first and second residues may be accomplished by a variety of mechanisms. For example, the bond may be cleaved by an enzyme in the kidney.

The residue providing the first component may be characterized as the "AII antagonist active" residue. Such "active" residue may be provided by a compound having AII antagonist activity or by a metabolite of such compound having AII antagonist activity. The residue providing the second component may be characterized in being capable of forming a cleavable bond connecting the "active" first residue and the second residue. Such bond is cleavable by

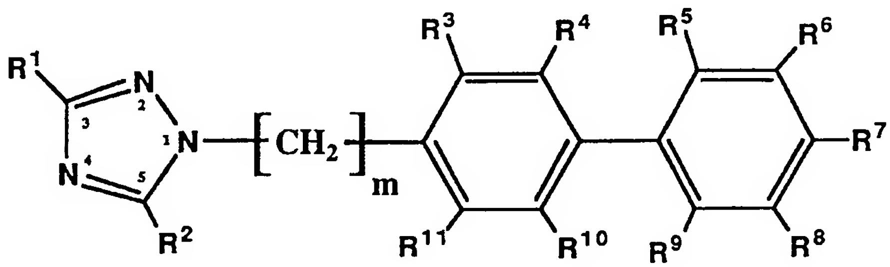
an enzyme located in the kidney. In a preferred embodiment, this cleavable bond is typically a hydrolyzable amide bond, that is, a bond between a carbonyl-terminated moiety and an reactive nitrogen-terminated moiety, such as an amino-terminated moiety, which may be cleaved by enzyme found in the kidney, but which is not cleaved substantially by enzymes located in other organs or tissues of the body. Preferred bond-cleaving enzymes would be found predominantly in the kidney.

The conjugate containing the residue of an AII antagonist compound and containing the cleavable fragment or residue may possess AII antagonist activity comparable to, or more than, or less than, the AII antagonist compound which forms the conjugate. In one embodiment of the invention, the conjugate will have AII receptor blocking activity comparable to the AII antagonist component forming the conjugate. In another embodiment of the invention, the conjugate will have AII receptor blocking activity less than the AII receptor blocking activity forming the conjugate. One advantage of such differential activity between the conjugate and the AII antagonist component is that certain side effects associated with non-renal, systemic AII receptor blocking may be avoided or reduced. For example, at least one conjugate of the invention has been found to have very large differential in AII receptor blocking activities between the conjugate and the AII antagonist component forming the conjugate. Such differential activity is advantageous in that therapeutically-effective antihypertensive doses of the conjugate may be administered to give renal-selective AII receptor blocking action resulting from kidney-specific enzyme hydrolysis or metabolism of the conjugate to free the active AII receptor blocker within the kidney. Inasmuch as this renal-selective conjugate has relatively low AII receptor blocking activity, compared to the AII receptor compound forming the conjugate, this conjugate will have fewer adverse side effects associated with

unwanted systemic interaction with non-renal AII receptors such as found in the vascular bed.

DETAILED DESCRIPTION OF THE INVENTION

The first residue of the conjugate may be selected from any class of compounds, or metabolites thereof, having angiotensin II antagonist activity. An example of one such class of angiotensin II antagonist compounds is provided by a class of biphenylalkyl 1H-substituted-1,2,4-triazole compounds defined by Formula I:

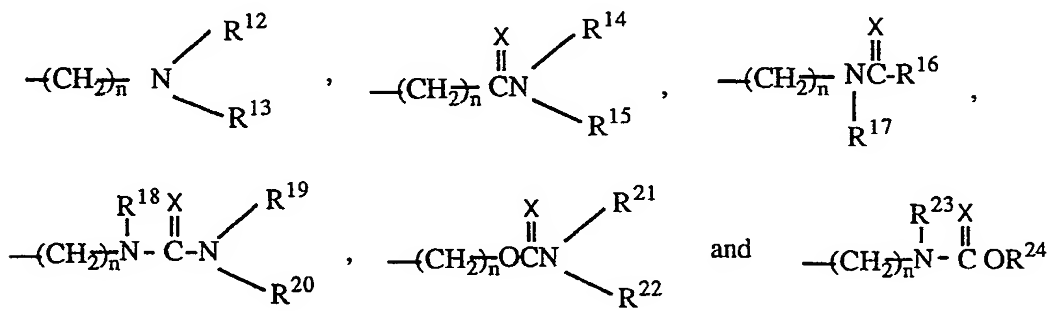


(I)

wherein m is a number selected from one to four, inclusive;

wherein each of R^1 through R^{11} is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy,

aralkylthiocarbonylthio, alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing groups has one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{16} and R^{17} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially

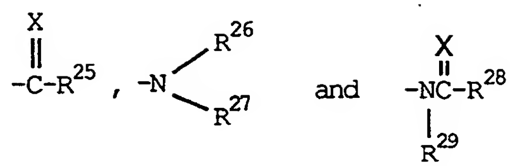
unsaturated; wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

and wherein each of R^3 through R^{11} may be further independently selected from hydroxy and from acidic moieties of the formula

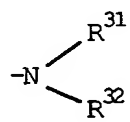
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

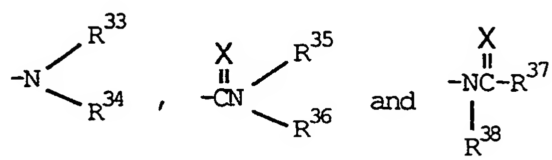
and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein each of R^{25}, R^{26}, R^{27}, R^{28} and R^{29} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, DR^{30} and



wherein D is selected from oxygen atom and sulfur atom and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each of R^{33}, R^{34}, R^{35}, R^{36}, R^{37} and R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl,

haloalkylsulfonyl, aralkyl and aryl, and wherein R^{26} and R^{27} taken together and R^{28} and R^{29} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{26} and R^{27} taken together and R^{31} and R^{32} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety.

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

Conjugates of the invention are therapeutically effective in treatment of cardiovascular disorders by acting directly on, or by providing cleavable components selected from Formula I compounds which act directly on, or as antagonists to, or as blockers of, the angiotensin II (AII) receptor. Thus, conjugates of Formula I would be therapeutically effective in treatment of cardiovascular disorders or would be precursors to, or prodrugs of, therapeutically-effective compounds.

Preferred compounds of Formula I, from which a cleavable component may be selected, are all characterized in having a substituent, other than hydrido, at each of the three- and five-positions of the triazole ring. Such substituents are selected from the aforementioned R^1 and R^2

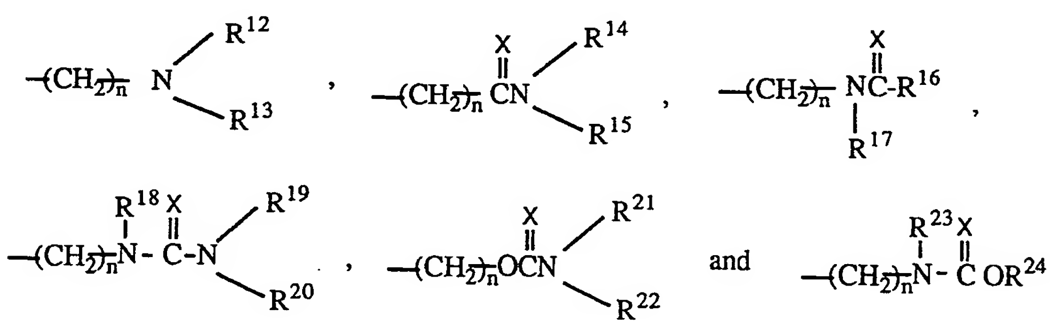
groups. Also especially useful are compounds having one of the R^1 and R^2 substituents selected from alkylcarbonyl, monoalkoxyalkyl, dialkoxyalkyl and difluoroalkyl groups. When the selected substituent for R^1 and R^2 is difluoroalkyl, then it is particularly useful for both of the fluoro atoms of the difluoroalkyl group to be substituted on the difluoroalkyl group carbon atom attached at the R^1 or R^2 positions of the triazole ring. Such difluoroalkyl group may be characterized as an "alpha-carbon difluoro-substituted difluoroalkyl group", or as an "alpha,alpha-difluoro-substituted alkyl group". When the selected substituent for R^1 or R^2 is monoalkoxyalkyl or dialkoxyalkyl, then it is particularly useful for the single alkoxy group or the two alkoxy groups, respectively, to be substituted on the carbon atom of the selected substituent which is attached at the R^1 or R^2 positions of the triazole ring. Such alkoxyalkyl groups may be characterized as "alpha-carbon monoalkoxy- or dialkoxy-substituted alkoxyalkyl groups", respectively, or "alpha-monoalkoxy-substituted or alpha,alpha-dialkoxy-substituted alkyl groups", respectively. When the selected substituent is alkylcarbonyl, then it is particularly useful for the carbonyl group to be attached at the R^1 or R^2 positions of the triazole ring. Such alkylcarbonyl group may be characterized as an "alpha-oxo-substituted alkyl group", and may be exemplified by the substituents 1-oxoethyl, 1-oxopropyl and 1-oxobutyl. Where compounds of Formula I contain any of these above-mentioned particularly-useful alpha-carbon substituted R^1 or R^2 groups at the triazole ring three- or five-position, it is preferred that such particularly-useful group be attached at the three-position, that is, as an R^1 substituent.

The phrase "acidic group selected to contain at least one acidic hydrogen atom", as used to define the $-Y_nA$ moiety, is intended to embrace chemical groups which, when attached to any of the R^3 through R^{11} positions of Formula I, confers acidic character to the compound of Formula I.

"Acidic character" means proton-donor capability, that is, the capacity of the compound of Formula I to be a proton donor in the presence of a proton-receiving substance such as water. Typically, the acidic group should be selected to have proton-donor capability such that the product compound of Formula I has a pK_a in a range from about one to about twelve. More typically, the Formula I compound would have a pK_a in a range from about two to about seven. An example of an acidic group containing at least one acidic hydrogen atom is carboxyl group (-COOH). Where n is zero and A is -COOH, in the $-Y_nA$ moiety, such carboxyl group would be attached directly to one of the R^3 through R^{11} positions. The Formula I compound may have one $-Y_nA$ moiety attached at one of the R^3 through R^{11} positions, or may have a plurality of such $-Y_nA$ moieties attached at more than one of the R^3 through R^{11} positions, up to a maximum of nine such $-Y_nA$ moieties. There are many examples of acidic groups other than carboxyl group, selectable to contain at least one acidic hydrogen atom. Such other acidic groups may be collectively referred to as "bioisosteres of carboxylic acid" or referred to as "acidic bioisosteres". Specific examples of such acidic bioisosteres are described hereinafter. Compounds of Formula I having the $-Y_nA$ moiety attached at one of positions R^5, R^6, R^8 and R^9 would be expected to have preferred properties, while attachment at R^5 or R^9 would be more preferred.

A preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R^1 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl,

aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino,

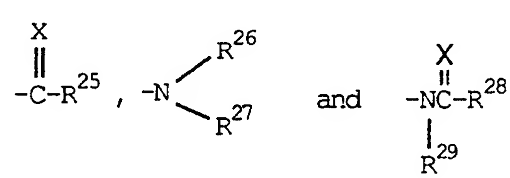
monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be further independently selected from hydroxy and from acidic moieties of the formula

$$-Y_nA$$

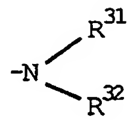
wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula

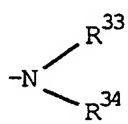
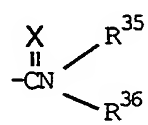
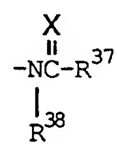


wherein X is selected from oxygen atom and sulfur atom; wherein each of R^{25}, R^{26}, R^{27}, R^{28} and R^{29} is selected from

hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula

 ,  and 

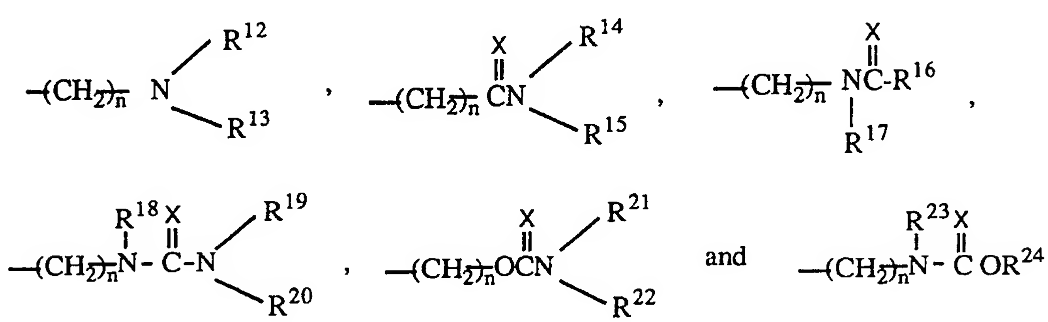
wherein X is selected from oxygen atom or sulfur atom;

wherein each of R^{33} through R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

A more preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R^1 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalklylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

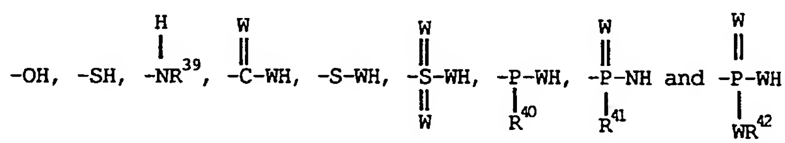
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be an further independently selected from hydroxy and from acidic moieties of the formula

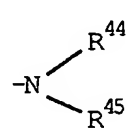
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive;

wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{40}, R^{41}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39}, R^{40}, R^{41} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group

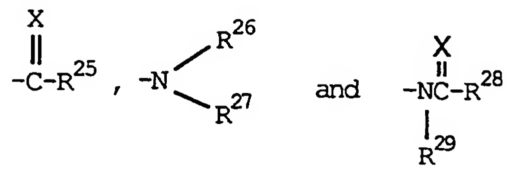
having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R^{44} and R^{45} may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

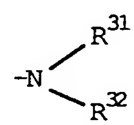
wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy,

aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein each of R^{25}, R^{26}, R^{27}, R^{28} and R^{29} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, wherein R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl;

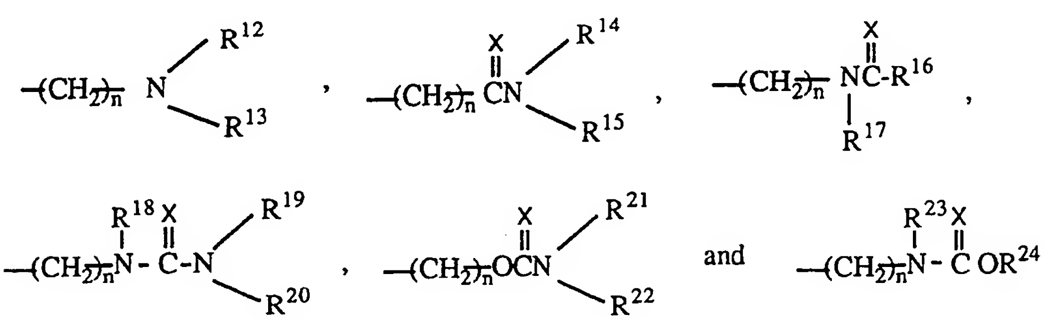
wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

An even more preferred class of compounds within the sub-class defined by Formula I consists of those

compounds wherein m is one; wherein each of R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino,

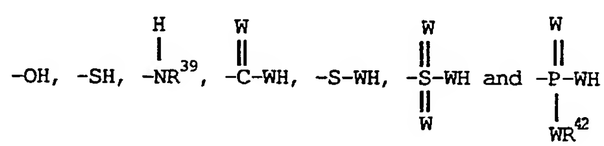
monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

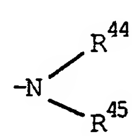
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

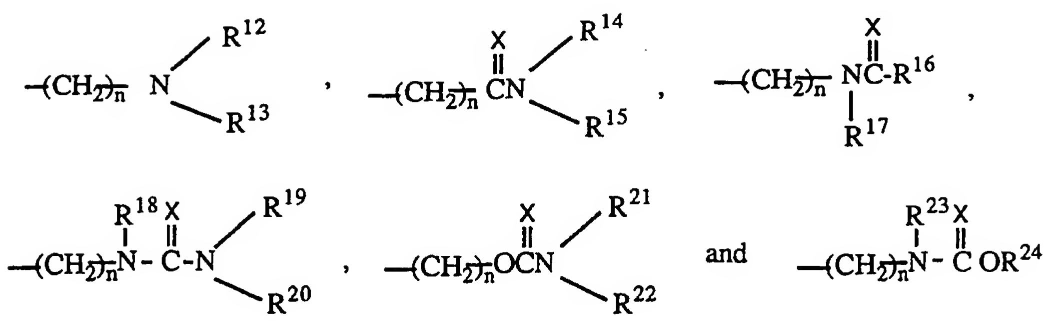
wherein each of R^1 through R^{11}, Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl,

difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

A highly preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

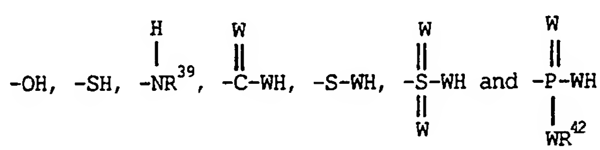
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio, mercapto and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

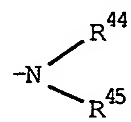
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

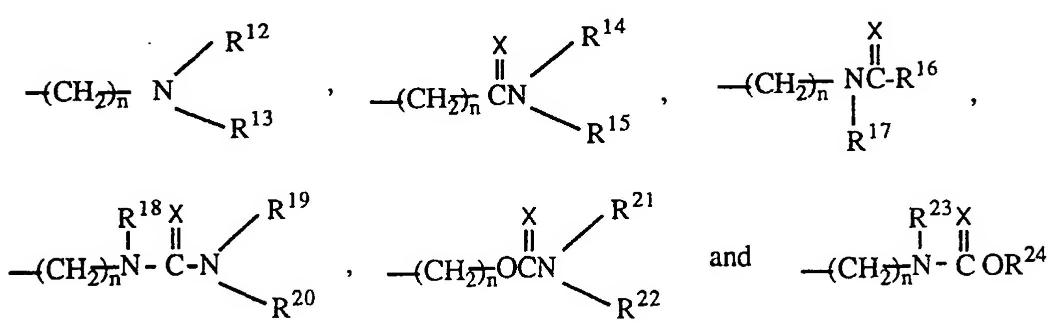
wherein each of R^1 through R^{11}, Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl,

cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

An even more highly preferred class of compounds within Formula I consists of those compounds wherein m is one; wherein each of R^1 and R^2 is independently selected from alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole, tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula



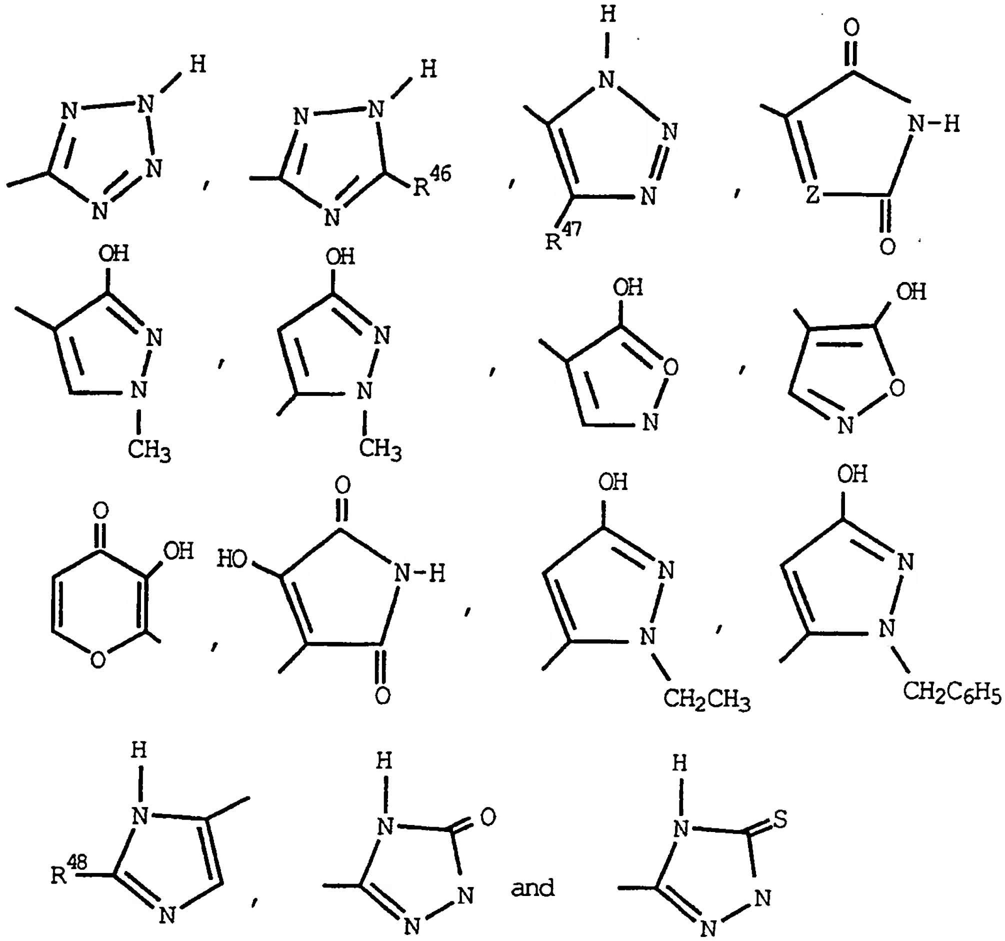
wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

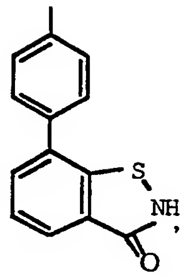
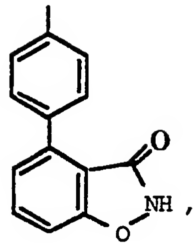
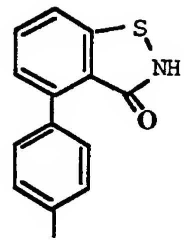
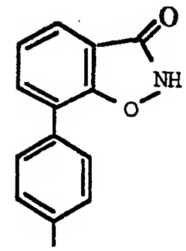
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

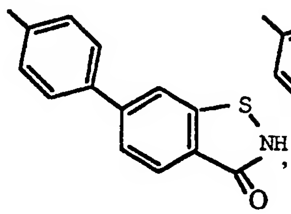
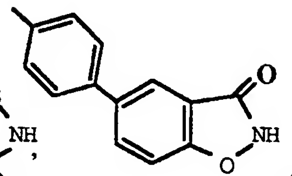
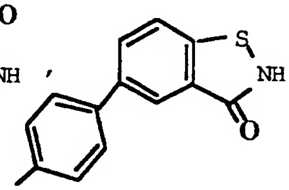
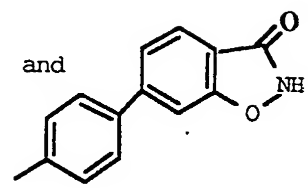
wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties consisting of CO_2H, CO_2CH_3, SH, CH_2SH, C_2H_4SH, PO_3H_2, $NHSO_2CF_3$, $NHSO_2C_6F_5$, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, $CONHOCH_3$, $CONHOC_2H_5$, $CONHCF_3$, OH, CH_2OH, C_2H_4OH, OPO_3H_2, OSO_3H ,



wherein each of R^{46}, R^{47} and R^{48} is independently selected from H, Cl, CN, NO_2, CF_3, C_2F_5, C_3F_7, CHF_2, CH_2F, CO_2CH_3, $CO_2C_2H_5$, SO_2CH_3, SO_2CF_3 and $SO_2C_6F_5$; wherein Z is selected from O, S, NR^{49} and CH_2; wherein R^{49} is selected from hydrido, CH_3 and $CH_2C_6H_5$; and wherein said acidic moiety may be a heterocyclic acidic group attached at any two adjacent positions of R^3 through R^{11} so as to form a fused ring system so as to include one of the phenyl rings of the biphenyl moiety of Formula I, said biphenyl fused ring system selected from

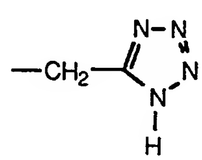
   and 

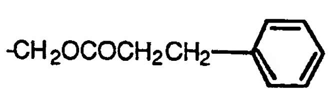
and the esters, amides and salts of said acidic moieties;

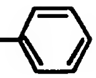
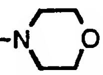
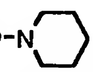
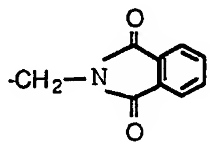
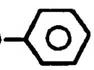
with the proviso that at least one of said R^1 through R^{24} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

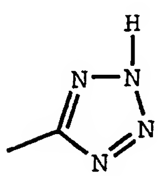
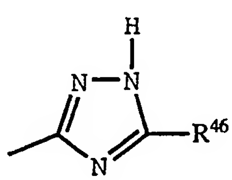
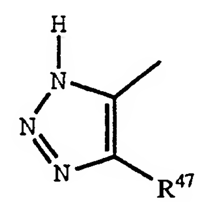
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R^1 and R^2 is independently selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO,

CH_2CO_2H, $CH(CH_3)CO_2H$, NO_2, Cl,  ,

, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$,

$-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H, $-CH_2CH_2-CO-$, $-CH_2CH_2CO-$, $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2OCSNHCH_3$, $-CH_2NHCSOC_3H_7$, $-CH_2CH_2CH_2F$, $-CH_2ONO_2$, , $-CH_2SH$, $-CH_2O-$, H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

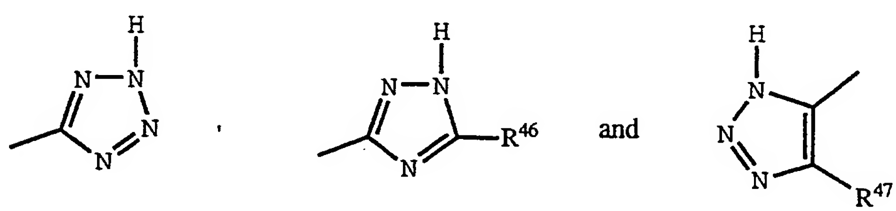
 ,  and 

wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

A class of compounds of more particular interest within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein R^1 is selected from amino, aminomethyl, aminoethyl, aminopropyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein R^2 is selected from ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, 4-methylbutyl, tert-butyl, n-pentyl and neopentyl; wherein each of R^3, R^4, R^6, R^7, R^8, R^{10}, and R^{11} is hydrido; wherein one of R^5 and R^9 is hydrido and the other of R^5 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

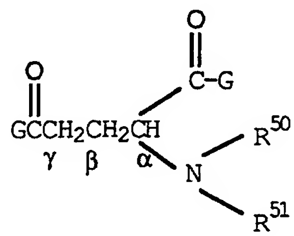


wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

The second component of a conjugate of the invention is provided by a residue which forms a kidney-enzyme-cleavable amide bond with the residue of the first-component AII antagonist compound. Such residue is preferably selected from a class of compounds of Formula II:

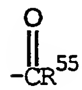


(II)

wherein each of R^{50} and R^{51} may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-OR^{52}$, $-SR^{53}$ and $>NR^{54}$ with each of R^{52}, R^{53} and R^{54} independently selected from alkyl; and wherein R^{54} may be further selected from hydrido; with the proviso that said cleavable bond is within an amide group formed between said first and second residues, wherein said first residue has a terminal primary or second amino moiety provided by one of said R^1 through R^{11} substituents of said Formula I compound or provided by a linker group attached to one of said R^1-R^{11} substituents of said Formula I, and wherein said second residue has a carbonyl moiety attached at the gamma-position carbon of said Formula II compound, whereby said amide bond is formed from said first residue amino moiety and said second residue carbonyl moiety.

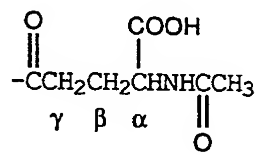
More preferred are compounds of Formula II wherein each G is hydroxy.

A more highly preferred class of compounds within Formula II consists of those compounds wherein each

G is hydroxy; wherein R^{50} is hydrido; and wherein R^{51} is selected from 

wherein R^{55} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

A most highly preferred compound of Formula II is N-acetyl-γ-glutamic acid which provides a residue for the second component of a conjugate of the invention as shown below:

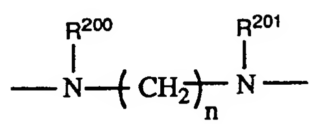


The phrase "terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino terminal moiety" characterizes a structural requirement for selection of a suitable angiotensin II antagonist compound as the "active" first residue of a conjugate of the invention. Such terminal amino moiety must be available to react with a terminal carboxylic moiety of the cleavable second residue to form a kidney-enzyme-specific hydrolyzable bond.

In one embodiment of the invention, the first component used to form a conjugate of the invention provides a first residue derived from an AII antagonist compound containing a terminal primary or secondary amino moiety. Examples of such terminal amino moiety are amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups such as aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

In another embodiment of the invention, the first component used to form the conjugate of the invention provides a first residue derived from an AII antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety. An example of a moiety convertible to an amino terminal moiety is a carboxylic acid group reacted with hydrazine so as to convert the acid moiety to carboxylic acid hydrazide. The hydrazide moiety thus contains the terminal amino moiety which may then be further reacted with the carboxylic acid containing residue of the second component to form a hydrolyzable amide bond. Such hydrazide moiety thus constitutes a "linker" group between the first and second components of a conjugate of the invention.

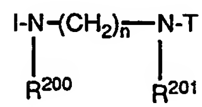
Suitable linker groups may be provided by a class of diamino-terminated linker groups based on hydrazine as defined by Formula III:



(III)

wherein each of R^{200} and R^{201} may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfino, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive. In Table I there is shown a class of specific examples of diamino-terminated linker groups within Formula III, identified as Linker Nos. 1-73. These linker groups would be suitable to form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of a carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

TABLE I



I = inhibitor
T = acetyl-γ-glutamyl

LINKER NO.	n	R^{200}	R^{201}
1	0	H	H
2	0	CH_3	H
3	0	C_2H_5	H
4	0	C_3H_7	H
5	0	$CH(CH_3)_2$	H
6	0	C_4H_9	H
7	0	$CH(CH_3)CH_2CH_3$	H
8	0	$C(CH_3)_3$	H
9	0	C_5H_9	H
10	0	C_6H_{11} (cyclo)	H
11	0	C_6H_5	H
12	0	$CH_2C_6H_5$	H
13	0	H	CH_3

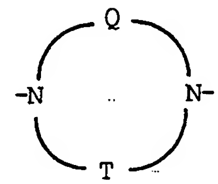
LINKER NO.	n	R^{200}	R^{201}
14	0	H	C_2H_5
15	0	H	C_3H_7
16	0	H	$CH(CH_3)_2$
17	0	H	C_4H_9
18	0	H	$CH(CH_3)CH_2CH_3$
19	0	H	$C(CH_3)_3$
20	0	H	C_5H_9
21	0	H	C_6H_{13}
22	0	H	C_6H_5
23	0	H	$CH_2C_6H_5$
24	0	H	C_6H_{11} (cyclo)
25	0	C_6H_{13}	H
26	0	CH_3	CH_3
27	0	C_2H_5	C_2H_5
28	0	C_3H_7	C_3H_7
29	0	$CH(CH_3)_2$	$CH(CH_3)_2$
30	0	C_4H_9	C_4H_9
31	0	$CH(CH_3)CH_2CH_3$	$CH(CH_3)CH_2CH_3$

LINKER NO.	n	R^{200}	R^{201}
32	0	$C(CH_3)_3$	$C(CH_3)_3$
33	0	C_5H_9	C_5H_9
34	0	C_6H_{13}	C_6H_{13}
35	0	C_6H_{11} (cyclo)	C_6H_{11} (cyclo)
36	0	C_6H_5	C_6H_5
37	0	$CH_2C_6H_5$	$CH_2C_6H_5$
38	3	H	H
39	3	CH_3	H
40	3	H	CH_3
41	3	C_6H_5	H
42	3	H	C_6H_5
43	3	CH_3	C_6H_5
44	3	C_6H_5	CH_3
45	3	$CH_2C_6H_5$	H
46	3	H	$CH_2C_6H_5$
47	4	H	H
48	4	CH_3	H

LINKER NO.	n	R^{200}	R^{201}
49	4	H	CH_3
50	4	C_6H_5	H
51	4	H	C_6H_5
52	4	CH_3	C_6H_5
53	4	C_6H_5	CH_3
54	4	$CH_2C_6H_5$	H
55	4	H	$CH_2C_6H_5$
56	5	H	H
57	5	CH_3	H
58	5	H	CH_3
59	5	C_6H_5	H
60	5	H	C_6H_5
61	5	CH_3	C_6H_5
62	5	C_6H_5	CH_3
63	5	$CH_2C_6H_5$	H
64	5	H	$CH_2C_6H_5$
65	6	H	H

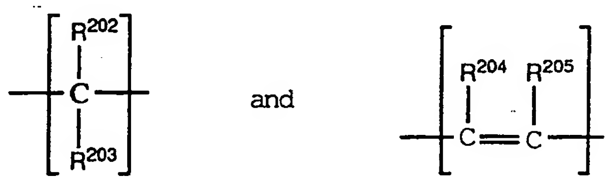
LINKER NO.	n	R^{200}	R^{201}
66	6	CH_3	H
67	6	H	CH_3
68	6	C_6H_5	H
69	6	H	C_6H_5
70	6	CH_3	C_6H_5
71	6	C_6H_5	CH_3
72	6	$CH_2C_6H_5$	H
73	6	H	$CH_2C_6H_5$

Another class of suitable diamino terminal linker groups is defined by Formula IV:



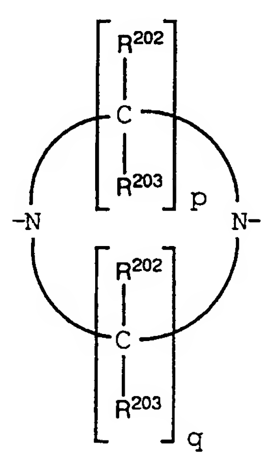
(IV)

wherein each of Q and T is one or more groups independently selected from



wherein each of R^{202} through R^{205} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

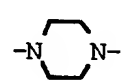
A preferred class of linker groups within Formula IV is defined by Formula V:



(V)

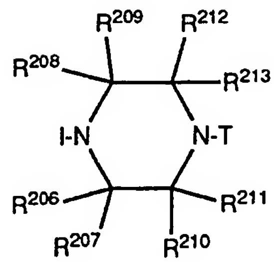
wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R^{202} and R^{203} is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R^{202} or R^{203} is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

A more preferred class of linker groups of Formula V consists of divalent radicals wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive. Even more preferred are linker groups wherein each of R^{202} and R^{203} is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three. Most preferred is a linker group wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two; such most preferred linker group is derived from a piperazinyl group and has the structure



In Table II there is shown a class of specific examples of cyclized, diamino-terminated linker groups within Formula V. These linker groups, identified as Linker Nos. 74-95, would be suitable to form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

TABLE II

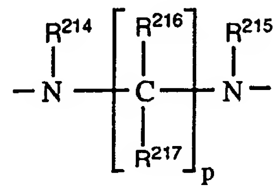


I = inhibitor
T = acetyl-γ-glutamyl

LINKER NO.	R^{206}	R^{207}	R^{208}	R^{209}	R^{210}	R^{211}	R^{212}	R^{213}
74	H	H	H	H	H	H	H	H
75	CH_3	H	H	H	H	H	H	H
76	H	H	H	H	CH_3	H	H	H
77	CH_3	H	H	H	CH_3	H	H	H
78	CH_3	H	CH_3	H	H	H	H	H
79	CH_3	H	H	H	H	H	CH_3	H
80	CH_3	CH_3	H	H	H	H	H	H
81	H	H	H	H	CH_3	CH_3	H	H
82	CH_3	CH_3	H	H	CH_3	CH_3	H	H
83	CH_3	CH_3	CH_3	CH_3	H	H	H	H
84	CH_3	CH_3	H	H	H	H	CH_3	CH_3
85	H	H	H	H	CH_3	CH_3	CH_3	CH_3

LINKER NO.	R^{206}	R^{207}	R^{208}	R^{209}	R^{210}	R^{211}	R^{212}	R^{213}
86	C_6H_5	H	H	H	H	H	H	H
87	H	H	H	H	C_6H_5	H	H	H
88	C_6H_5	H	H	H	C_6H_5	H	H	H
89	C_6H_5	H	H	H	H	H	C_6H_5	H
90	C_6H_5	H	C_6H_5	H	H	H	H	H
91	$CH_2C_6H_5$	H	H	H	H	H	H	H
92	H	H	H	H	$CH_2C_6H_5$	H	H	H
93	$CH_2C_6H_5$	H	H	H	$CH_2C_6H_5$	H	H	H
94	$CH_2C_6H_5$	H	H	H	H	H	$CH_2C_6H_5$	H
95	$CH_2C_6H_5$	H	$CH_2C_6H_5$	H	H	H	H	H

Another class of suitable diamino terminal linker groups is defined by Formula VI:

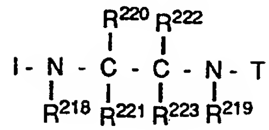


(VI)

wherein each of R^{214} through R^{217} is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfino, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

A preferred class of linker groups within Formula VI consists of divalent radicals wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{62} and R^{63} is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three. A more preferred class of linker groups within Formula VI consists of divalent radicals wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido and alkyl; and wherein p is two. A specific example of a more preferred linker within Formula VI is the divalent radical ethylenediamino. In Table III there is shown a class of specific examples of diamino-terminated linker gorups within Formula VI. These linker groups, identified as Linker Nos. 96-134, would be suitable to form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

TABLE III



I = inhibitor
G = acetyl-γ-glutamyl

LINKER NO.	R^{218}	R^{219}	R^{220}	R^{221}	R^{222}	R^{223}
96	H	H	H	H	H	H
97	H	H	H	H	H	CH_3
98	H	H	H	CH_3	H	H
99	H	H	H	CH_3	H	CH_3
100	CH_3	H	H	H	H	H
101	H	CH_3	H	H	H	H
102	H	H	H	H	CH_3	CH_3
103	H	H	CH_3	CH_3	H	H
104	CH_3	CH_3	H	H	H	H
105	H	H	H	H	H	C_6H_5
106	H	H	H	C_6H_5	H	H
107	H	H	H	C_6H_5	H	C_6H_5
108	C_6H_5	H	H	H	H	H

LINKER NO.	R^{218}	R^{219}	R^{220}	R^{221}	R^{222}	R^{223}
109	H	C_6H_5	H	H	H	H
110	H	H	H	H	C_6H_5	C_6H_5
111	H	H	C_6H_5	C_6H_5	H	H
112	C_6H_5	C_6H_5	H	H	H	H
113	H	H	H	H	H	C_2H_5
114	H	H	H	C_2H_5	H	H
115	H	H	H	C_2H_5	H	C_2H_5
116	C_2H_5	H	H	H	H	H
117	H	C_2H_5	H	H	H	H
118	H	H	H	H	C_2H_5	C_2H_5
119	H	H	C_2H_5	C_2H_5	H	H
120	C_2H_5	C_2H_5	H	H	H	H
121	CH_3	H	C_6H_5	H	H	H
122	CH_3	H	H	H	C_6H_5	H
123	H	CH_3	C_6H_5	H	H	H
124	H	CH_3	H	H	C_6H_5	H
125	CH_3	CH_3	H	C_6H_5	H	H

LINKER NO.	R^{218}	R^{219}	R^{220}	R^{221}	R^{222}	R^{223}
126	CH_3	CH_3	H	H	H	C_6H_5
127	H	H	H	H	H	$CH_2C_6H_5$
128	H	H	H	$CH_2C_6H_5$	H	H
129	$CH_2C_6H_5$	H	H	H	H	H
130	H	$CH_2C_6H_5$	H	H	H	H
131	CH_3	H	$CH_2C_6H_5$	H	H	H
132	CH_3	H	H	H	$CH_2C_6H_5$	H
133	H	CH_3	$CH_2C_6H_5$	H	H	H
134	H	CH_3	H	H	$CH_2C_6H_5$	H

The term "hydrido" denotes a single hydrogen atom (H). This hydrido group may be attached, for example, to a carbon atom to form a CH< group or attached to an oxygen atom to form a hydroxyl group; or as another example, two hydrido groups may be attached to a carbon atom to form a $-CH_2-$ group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atomms. The term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl and cyclobutyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a fluoro atom within the group. Dihaloalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two fluoro atoms, such as difluoromethyl and difluorobutyl groups, or two chloro atoms, such as a dichloromethyl group, or one fluoro atom and one chloro atom, such as a fluoro-chloromethyl group. Examples of a polyhaloalkyl are trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3-tetrafluoropropyl groups. The term "difluoroalkyl" embraces alkyl groups having two fluoro atoms substituted on any one or two of the alkyl group carbon atoms. Preferably, when the difluoroalkyl group is attached at the triazole ring R^1 and R^2 positions of Formula I, the two

fluoro atoms are substituted on the carbon atom which is attached directly to the triazole ring. Such preferred difluoroalkyl group may be characterized as an "alpha-carbon difluoro-substituted difluoroalkyl group" The terms "alkylol" and "hydroxyalkyl" embrace linear or branched alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to about ten carbon atoms, and containing at least one carbon-carbon double bond, which carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety. The term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon triple bond. The term "cycloalkenyl" embraces cyclic radicals having three to about ten ring carbon atoms including one or more double bonds involving adjacent ring carbons. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy group. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy groups attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl groups. The term "alkylthio" embraces radicals containing a linear or branched alkyl group, of one to about ten carbon atoms attached to a divalent sulfur atom, such as a methythio group. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl and biphenyl. Preferred aryl groups are those consisting of one, two, or three benzene rings. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, phenylbutyl and diphenylethyl. The terms "benzyl" and "phenylmethyl" are

interchangeable. The terms "aryloxy" and "arylthio" denote radical respectively, aryl groups having an oxygen or sulfur atom through which the radical is attached to a nucleus, examples of which are phenoxy and phenylthio. The terms "sulfinyl" and "sulfonyl", whether used alone or linked to other terms, denotes respectively divalent radicals SO and SO_2. The term "aralkoxy", alone or within another term, embraces an aryl group attached to an alkoxy group to form, for example, benzyloxy. The term "acyl" whether used alone, or within a term such as acyloxy, denotes a radical provided by the residue after removal of hydroxyl from an organic acid, examples of such radical being acetyl and benzoyl. The term "heteroaryl" embraces aromatic ring systems containing one or two hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five or six ring members, examples of which are thienyl, furanyl, pyridinyl, thiazolyl, pyrimidyl and isoxazolyl. Such heteroaryl may be attached as a substituent through a carbon atom of the heteroaryl ring system, or may be attached through a carbon atom of a moiety substituted on a heteroaryl ring-member carbon atom, for example, through the methylene substituent of imidazolemethyl moiety. Also, such heteroaryl may be attached through a ring nitrogen atom as long as aromaticity of the heteroaryl moiety is preserved after attachment. The term "amido" denotes a radical consisting of a nitrogen atom attached to a carbonyl group, which radical may be further substituted in the manner described herein. The amido radical can be attached to the nucleus of a compound of the invention through the carbonyl moiety or the nitrogen atom of the amido radical. The term "alkenylalkyl" denotes a radical having a double-bond unsaturation site between two carbons, and which radical may consist of only two carbons or may be further substituted with alkyl groups which may optionally contain additional double-bond unsaturation. For any of the foregoing defined radicals, preferred radicals are those containing between one and about ten carbon atoms.

Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, methylbutyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a plurality or unsaturated bonds, with such plurality of bonds either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

Conjugates of the invention formed from compounds of Formula I have been found to inhibit the action of angiotensin II in mammals. Thus, conjugates of Formula I are therapeutically useful in methods for treating hypertension by administering to a hypertensive patient a therapeutically-effective amount of a conjugate containing a compound of Formula I, such that the conjugate is hydrolyzed by an enzyme found predominantly in the kidney so as to release an active angiotensin II antagonist species. The phrase "hypertensive patient" means, in this context, a mammalian subject suffering from the effects of hypertension or susceptible to a hypertensive condition if not treated to prevent or control such hypertension.

Included within the invention are conjugates of compounds of Formula I which are tautomeric forms of the described compounds, isomeric forms including diastereoisomers, and the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected

from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicyclic, phenylacetic, mandelic, embonic (pamoic), methansulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic, cyclohexylaminosulfonic, stearic, algenic, β-hydroxybutyric, malonic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminium, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I. Also, such pharmaceutical salts may be formed with either a compound of Formula I which is contained in the conjugate, or such salts may be formed with the conjugate itself.

Conjugates of the invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for

separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting conjugates with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active conjugates can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

The first and second residues are provided by precursor compounds having suitable chemical moieties which react together to form a cleavable bond between the first and second residues. For example, the precursor compound of one of the residues will have a reactable carboxylic acid moiety and the precursor of the other residue will have a reactable amino moiety or a moiety convertible to a reactable amino moiety, so that a cleavable amide bond may be formed between the carboxylic acid moiety and the amino moiety.

Conjugates of the invention may be prepared using precursors of highly active angiotensin II antagonists of Formula I. Examples of lesser active, suitable precursors are acid chloride, esters and amides of angiotensin II antagonists of Formula I. For example, ester precursors of angiotensin II antagonists may be reacted with hydrazine to provide an amino terminal moiety which then can be reacted with a glutamic acid derivative to form a conjugate of the invention. Such precursors or intermediates themselves may be relatively strong, relatively weak, or inactive as AII antagonists. Also, conjugates of the invention may be prepared using

angiotensin II antagonists lacking a reactive terminal amino moiety. Such angiotensin II antagonists may be modified to contain a terminal acid moiety which then may be connected to a glutamyl residue through a diamino-terminated linker group, such as shown in Tables I-III.

A family of specific angiotensin II antagonist compounds of Formula I, from which a suitable first component of the conjugate may be selected, consists of biphenylmethyl 1H-substituted-1,2,4-triazole compounds listed below having a carboxylic acid terminal moiety or carboxylic acid moiety modified to be a hydrazide terminal moiety. All such compounds are characterized in having such carboxylic acid at one of the R^5 through R^9 positions of Formula I. Those compounds having a terminal carboxylic moiety may be reacted with one of the aforementioned linker groups, such as a hydrazine or a piperazine linker, to provide an amino terminal moiety which can then be reacted with the carboxylic acid moiety of a second component of the conjugate, such as a glutamic acid residue to form an enzyme-cleavable bond. Specific examples of these compounds are listed below:

4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid, hydrazide;
4'-[(5-butyl-3-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3-butyl-5-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
methyl 4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylate;

4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-secbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-tertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-mercapto-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-thiomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-thioethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-thiopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-hydroxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-methoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-ethoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-propoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-butoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(2-cyclohexylethyl))-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexanoyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-butyl-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-phenyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-phenylmethyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3-butyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-benzoyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[3-butyl-5-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(3,5-dipropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(3,5-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-secbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-isobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-tertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-isopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-mercapto-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-thiomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-thioethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-thiopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-hydroxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-methoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-ethoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-propoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-propyl-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
5-[4'-[[5-propyl-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-propyl-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
5-[4'-[[5-propyl-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-propyl-3-phenyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-propyl-3-phenylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-propyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-propyl-3-benzoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-propyl-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-propyl-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-propyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-propyl-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-propyl-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-propyl-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-propyl-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-propyl-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[3,5-bis(heptafluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-propyl-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-propyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-propyl-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-diethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-secbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-isobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-tertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-isopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-mercapto-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-thiomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-thioethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-thiopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-hydroxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-methoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-ethoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-propoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-ethyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-ethyl-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-ethyl-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-ethyl-3-phenyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-ethyl-3-phenylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-ethyl-3-benzoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethpyl-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-ethyl-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-secbutyl-3-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-disecbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-isobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-tertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-isopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-mercapto-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-thiomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-thioethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-thiopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-hydroxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-methoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-ethoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-propoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-secbutyl-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-phenyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-phenylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-secbutyl-3-benzoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-secbutyl-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-isobutyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-secbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-diisobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-tertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-isopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-mercapto-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-thiomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-thioethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-thiopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-hydroxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-methoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-ethoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-propoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-isobutyl-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-phenyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-phenylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isobutyl-3-benzoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isobutyl-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-tertbutyl-3-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-secbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-isobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-ditertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-isopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-mercapto-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-thiomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-thioethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-thiopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-hydroxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-methoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-ethoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-propoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-tertbutyl-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-phenyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-phenylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-tertbutyl-3-benzoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-tertbutyl-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-pentyl-3-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-secbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-isobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-tertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dipentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-isopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-mercapto-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-thiomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-thioethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-thiopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-hydroxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-methoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-ethoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-propoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-pentyl-3-phenyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-phenylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-pentyl-3-benzoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-isopentyl-3-secbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-isobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-tertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-diisopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-mercapto-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-thiomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-thioethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-thiopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-hydroxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-methoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-ethoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-propoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-pentyl-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-phenyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(5-isopentyl-3-phenylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-isopentyl-3-benzoyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-isopentyl-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-ethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-propyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-isopropyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-secbutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(1-butenyl)-3-isobutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-tertbutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-pentyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-isopentyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-mercapto-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-thiomethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-thioethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-thiopropyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-hydroxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-methoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-ethoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-propoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-cyclohexyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-phenyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-phenylmethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(1-butenyl)-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-benzoyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butenyl)-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-ethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-propyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-isopropyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-secbutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-isobutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-tertbutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-pentyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-isopentyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-mercapto-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-thiomethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-thioethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-thiopropyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-hydroxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-methoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-ethoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-propoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-cyclohexyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-phenyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-phenylmethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butenyl)-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butenyl)-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-ethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-propyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-isopropyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-secbutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-isobutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-tertbutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-pentyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-isopentyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(3-butenyl)-3-mercapto-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-thiomethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-thioethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-thiopropyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-hydroxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-methoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-ethoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-propoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-cyclohexyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-phenyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-phenylmethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-benzoyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(3-butenyl)-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butenyl)-3-(1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-ethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-propyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-secbutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-isobutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-tertbutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-pentyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-isopentyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-mercapto-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-thiomethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(1-butynyl)-3-thioethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-thiopropyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-hydroxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-methoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-ethoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-propoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-cyclohexyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-phenyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-phenylmethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-benzoyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(1-butynyl)-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(1-butynyl)-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-ethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-propyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-secbutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-isobutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-tertbutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-pentyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-isopentyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-mercapto-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-thiomethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-thioethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-thiopropyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butynyl)-3-hydroxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-methoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-ethoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-propoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-cyclohexyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-phenyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-phenylmethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-benzoyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(2-butynyl)-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(2-butynyl)-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-ethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-propyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-isopropyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-secbutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-isobutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-tertbutyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-isopentyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-pentyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-mercapto-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-thiomethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-thioethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-thiopropyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-hydroxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(3-butynyl)-3-methoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-ethoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-propoxy-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-cyclohexyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-cyclohexanoyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-phenyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-phenylmethyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-benzoyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(1,1-dimethoxypentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-(3-butynyl)-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-(3-butynyl)-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-diethoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dipropoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-diisopropoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dibutoxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dithiomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dithioethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dithiopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dithioisopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[3,5-di(1-butenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[3,5-di(2-butenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[3,5-di(3-butenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[3,5-di(1-butynyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[3,5-di(2-butynyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid; and
4'-[[3,5-di(3-butynyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid.

Another family of specific angiotensin II antagonist compounds of Formula I, from which a suitable first component of the conjugate may be selected, consists of biphenylmethyl 1H-substituted-1,2,4-triazole compounds listed below having an amino terminal moiety attached at the R^1 or R^2 positions of Formula I.. Such amino terminal moiety may be reacted directly with the carboxylic acid moiety of a second component of the conjugate, such as a glutamic acid residue to form an enzyme-cleavable bond. Specific examples of these compounds are listed below:

5-[4'-[(5-ethyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-ethyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-ethyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-ethyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-ethyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-ethyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-propyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-propyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-propyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-propyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-propyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-propyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-propyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-propyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-isopropyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-isopropyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-isopropyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-isopropyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-isopropyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopropyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-secbutyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-secbutyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-secbutyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-secbutyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-secbutyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isobutyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-isobutyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isobutyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isobutyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isobutyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-tertbutyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-tertbutyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-tertbutyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-tertbutyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-tertbutyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-pentyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-pentyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-pentyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-pentyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-pentyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isopentyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isopentyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isopentyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isopentyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-isopentyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-hexyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-hexyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-hexyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-hexyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-hexyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-hexyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole; and
5-[4'-[[3-hexyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

Another family of specific angiotensin II antagonist compounds of Formula I, from which a suitable first component of the conjugate may be selected, consists of biphenylmethyl 1H-substituted-1,2,4-triazole compounds listed below having a terminal carboxylic acid moiety attached at the R^1 or R^2 positions of Formula I.. Those compounds having a terminal carboxylic moiety may be reacted with one of the aforementioned linker groups, such as a hydrazine or a piperazine linker, to provide an amino terminal moiety which can then be reacted with the carboxylic acid moiety of a second component of the conjugate, such as a glutamic acid residue to form an

enzyme-cleavable bond. Specific examples of these compounds are listed below:

5-[4'-[(5-ethyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-ethyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-ethyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-ethyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-ethyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-ethyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-propyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-propyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-propyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-propyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-propyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-propyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isopropyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-isopropyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-isopropyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-isopropyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-isopropyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopropyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-butyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-butyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-butyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-secbutyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-secbutyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-secbutyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-secbutyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-secbutyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-secbutyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isobutyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isobutyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isobutyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isobutyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-isobutyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isobutyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-tertbutyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-tertbutyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-tertbutyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-tertbutyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-tertbutyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-tertbutyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-tertbutyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-pentyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-pentyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-pentyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-pentyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-pentyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-pentyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-pentyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isopentyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isopentyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isopentyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isopentyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-isopentyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-isopentyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-isopentyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-hexyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-hexyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-hexyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-hexyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-hexyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-hexyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-hexyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole; and
5-[4'-[[3-hexyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

A family of specific angiotensin II antagonist compounds of highest interest within Formula I from which a suitable first component of the conjugate may be selected, consists of amino-terminated biphenylmethyl 1H-substituted-1,2,4-triazole compounds as listed below. Such compounds would be suitable to form a conjugate with a carboxylic moiety of a second component of the conjugate, such as a glutamic acid residue, to form an enzyme-cleavable amide bond by direct reaction or by reaction through a diamino-containing linker of the type mentioned above. These Formula I angiotensin II antagonist compounds of highest interest are as follows:

methyl 4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylate;
4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid, hydrazide;
4'-[(5-butyl-3-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3-butyl-5-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-secbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-tertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(2-cyclohexylethyl))-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexanoyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-phenyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-phenylmethyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-benzoyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-butyl-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[3-butyl-5-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dipropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-disecbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-diisobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-ditertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dipentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-diisopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
5-[4'-[(5-butyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-butyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-butyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole; and
5-[4'-[[3-butyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

General Synthetic Procedures

Conjugates of the invention are synthesized by reaction between precursors of the first and second residues. One of such precursors must contain a reactive acid moiety, and the other precursor must contain a reactive amino moiety, so that a conjugate is formed having a cleavable bond. Either precursor of the first and second residues may contain such reactive acid or amino moieties. Preferably, the precursors of the first residue are angiotensin II antagonists and will contain a reactive amino moiety or a moiety convertible to a reactive amino moiety. Inhibitor compounds lacking a reactive amino moiety may be chemically modified to provide such reactive amino moiety. Chemical modification of these inhibitor compounds lacking a reactive amino group may be accomplished by reacting an acid or an ester group on an AII antagonist compound with an amino compound having at least one reactive amino moiety and another reactive hetero atom selected from O, S and N. A suitable amino compound would be a diamino compound such as hydrazine or urea. Hydrazine, for example, may be reacted with a carboxylic acid or ester moiety of an AII antagonist compound to form a hydrazide derivative of such AII antagonist compound.

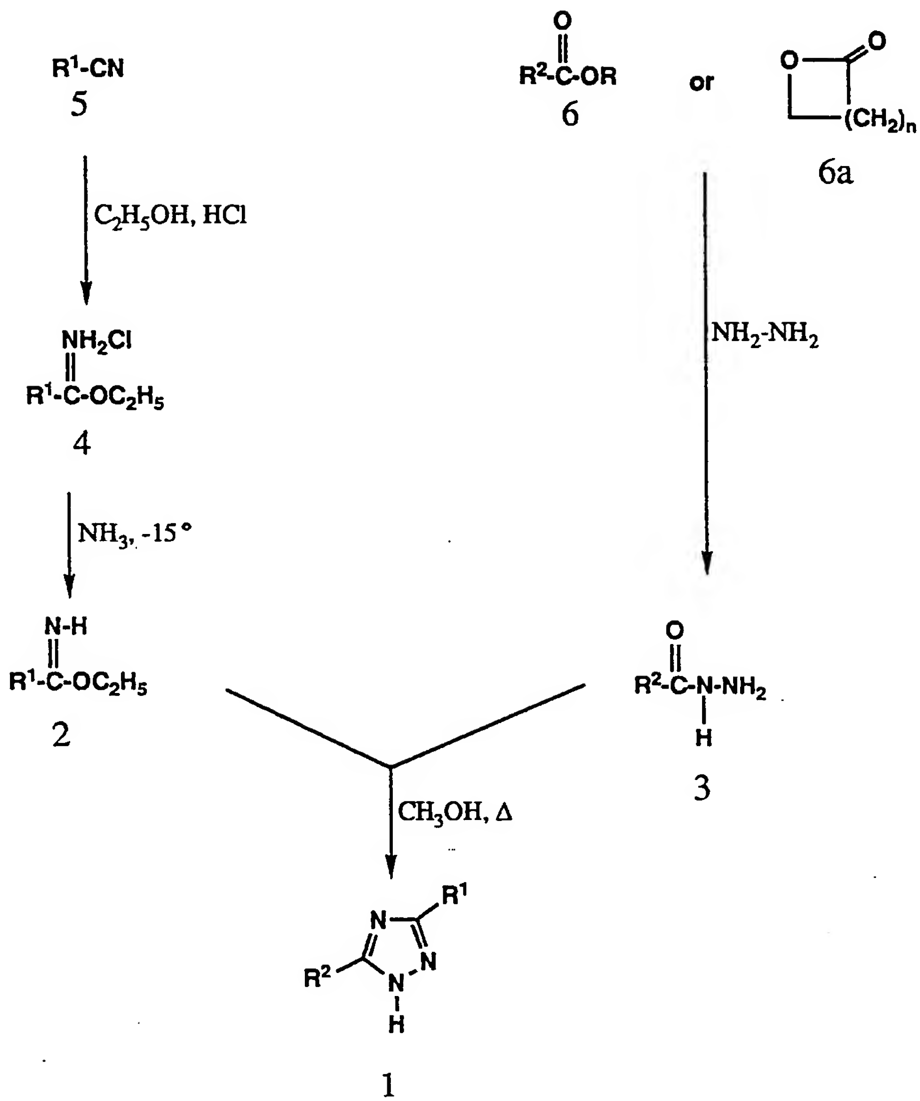
The AII antagonist compound 4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid may be used as a model compound to illustrate the chemical modification of a carboxylic acid-containing compound to make a reactive amino-containing precursor for synthesizing a conjugate of the invention. In the following General Synthetic Procedures, there are described firstly, in Schemes I-VI, methods for making suitable angiotensin II antagonists of Formula I for selection as the first component of the conjugate. Then, in Schemes VII-XII, there are described general methods for making a conjugate by reacting a first component AII antagonist of Formula I

with a cleavable second component represented by N-acetyl-γ-glutamic acid.

Conjugates of the invention may be prepared using precursors of highly active angiotensin II antagonists of Formula I. Examples of lesser active, suitable precursors are acid chloride, esters and amides of angiotensin II antagonists of Formula I. For example, ester precursors of more active angiotensin II antagonists, such as ester-type AII antagonists of Example Nos. 1, 34, 35, 67 and 68, as well as AII antagonists containing carboxylic acid terminal moieties, of Example Nos. 2, 6, 8, 18-20, 36, 52, 63, 64, 71-72 and 75-78, may be reacted with hydrazine to provide an intermediate bearing an amino terminal moiety which then can be reacted with a glutamic acid derivative to form a conjugate of the invention. Such precursors or intermediates themselves may be relatively strong, relatively weak, or inactive as AII antagonists. Also, conjugates of the invention may be prepared using angiotensin II antagonists lacking a reactive terminal acidic or amino moiety. Such angiotensin II antagonists, as shown in Example Nos. 3, 5, 7, 9-16, 21-33, 37-40, 42-51, 53-62, 65, 66, 69-70, 73 and 74, lack a terminal amino moiety. These AII antagonist compounds may be modified to contain a terminal amino moiety which then may be connected to a glutamyl residue through a diamino-terminated linker group, such as shown in Tables I-III.

C-2631/1

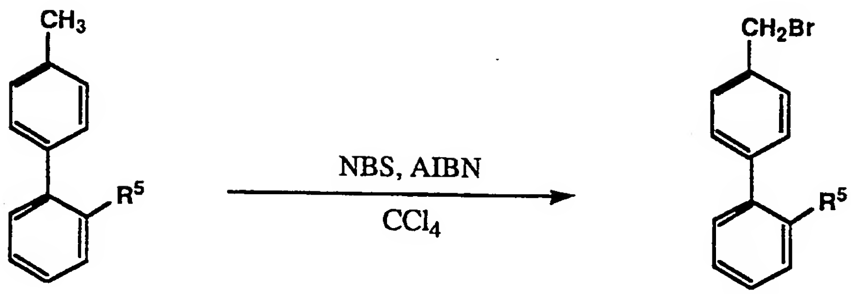
Scheme I



R = H, CH_3, or C_2H_5

Synthetic Scheme I shows the preparation of 1H-1,2,4-triazoles 1 from ethyl iminoesters 2 and the corresponding hydrazide 3 via the general proceure outlined by H. Paul, G. Hilgetog and G. Jahnchen, Chem. Ber., 101, 2033 (1968). The free, iminoesters 2 can be prepared from the corresponding iminoester hydrochlorides 4, which in turn can be prepared from the corresponding nitrile 5; the procedures for the preparation of 2 and 4 from 5 are outlined by P. Reynaud and R. D. Moreau, Bull. Soc. Chim. France, 2997 (1964). The hydrazides 3 can be either purchased or prepared from the corresponding alkyl esters 6 or lactones 6a and hydrazine.

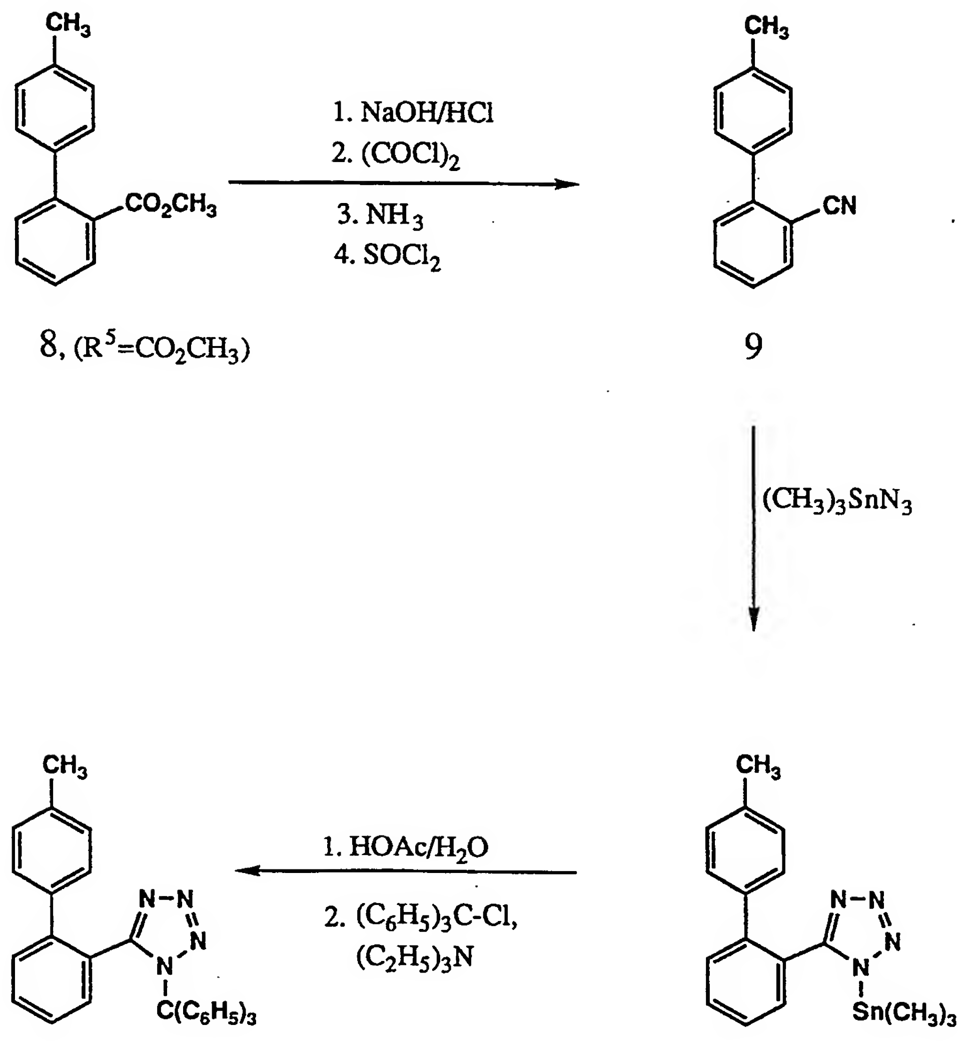
Scheme II



8 7

Synthetic Scheme II shows the preparation of the alkylating agent 7 from the corresponding precursor 8. When R^5 equals CO_2CH_3, 8 was purchased from Chemo Dynamics Inc.

Scheme III



8, (R^5=CO_2CH_3)

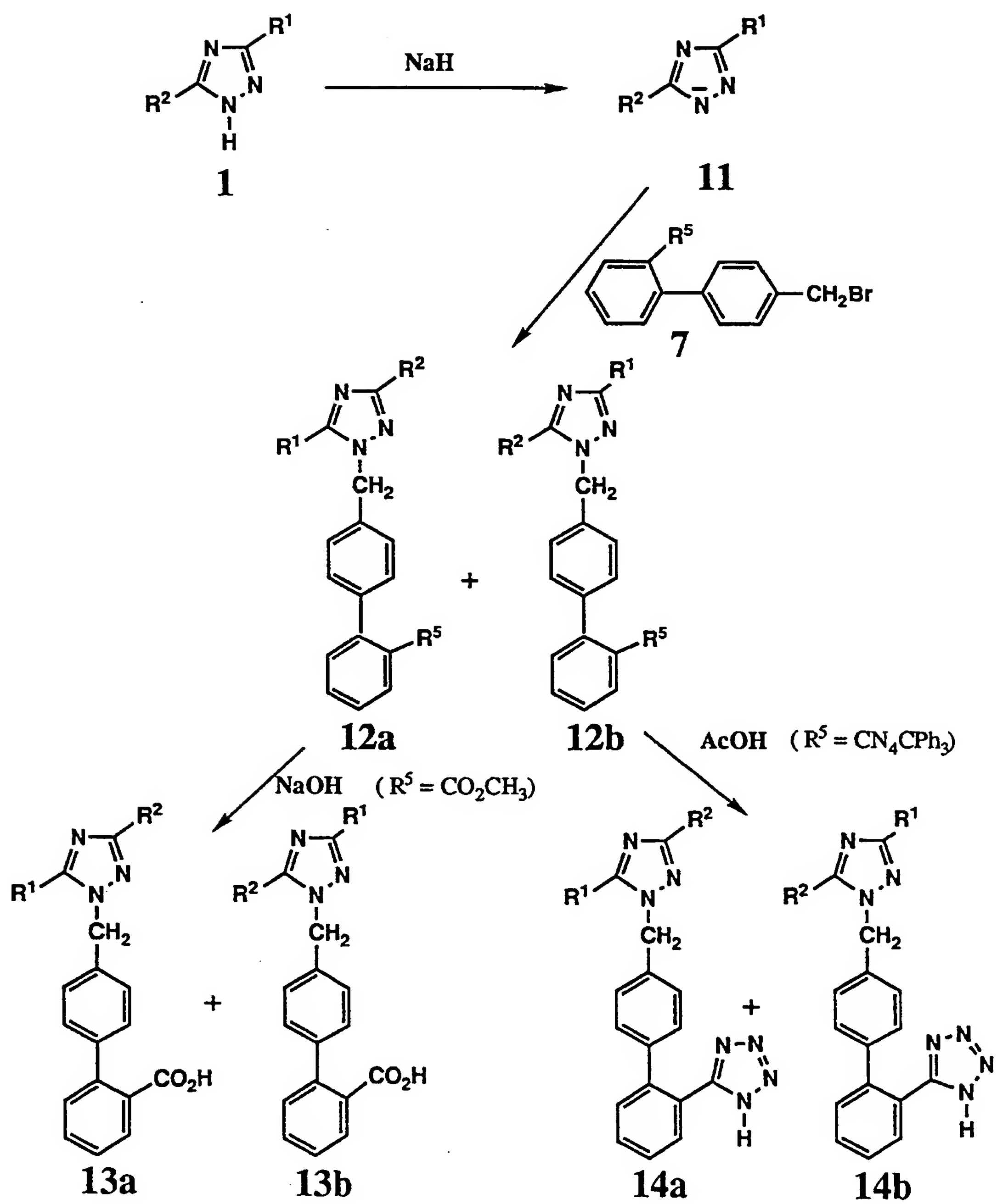
9

8, [R^5= $CN_4C(C_6H_5)_3$]

10

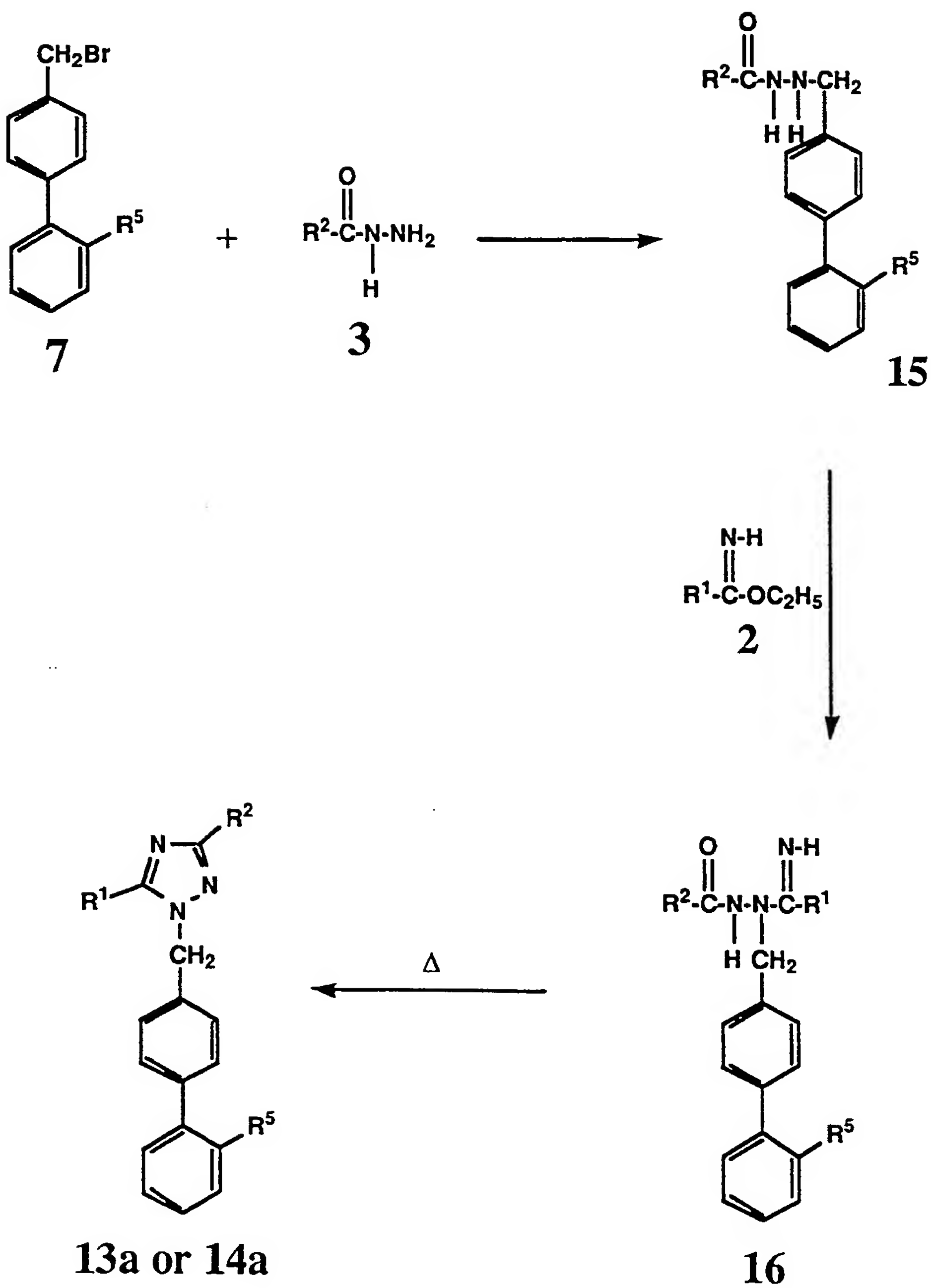
Synthetic Scheme III shows the preparation of the alkylating agent precursor 8 where R^5 equal $CN_4C(C_6H_5)_3$ from the corresponding methyl ester 8 (R^5=CO_2CH_3). In step 1, the methyl ester is converted to the corresponding acid (R^5=CO_2H) by the action of sodium hydroxide/hydrochloric acid. In step 2, the acid is converted to the corresponding acid chloride (R^5=COCl) by the action of oxalyl chloride. In step 3, the acid chloride is converted to the corresponding primary amide (R^5=$CONH_2$) by the action of ammonia. In step 4, the amide is converted to the corresponding nitrile 9 by the action of thionyl chloride at reflux. The nitrile 9 is reacted with trimethyltinazide in toluene at reflux to give the corresponding trimethytin protected tetrazole 10; deprotection with acetic acid/water and reprotection with triphenylmethyl chloride/triethylamine gives the N-trityl tetrazole 8 (R^5=$CN_4C(C_6H_5)_3$).

Scheme IV



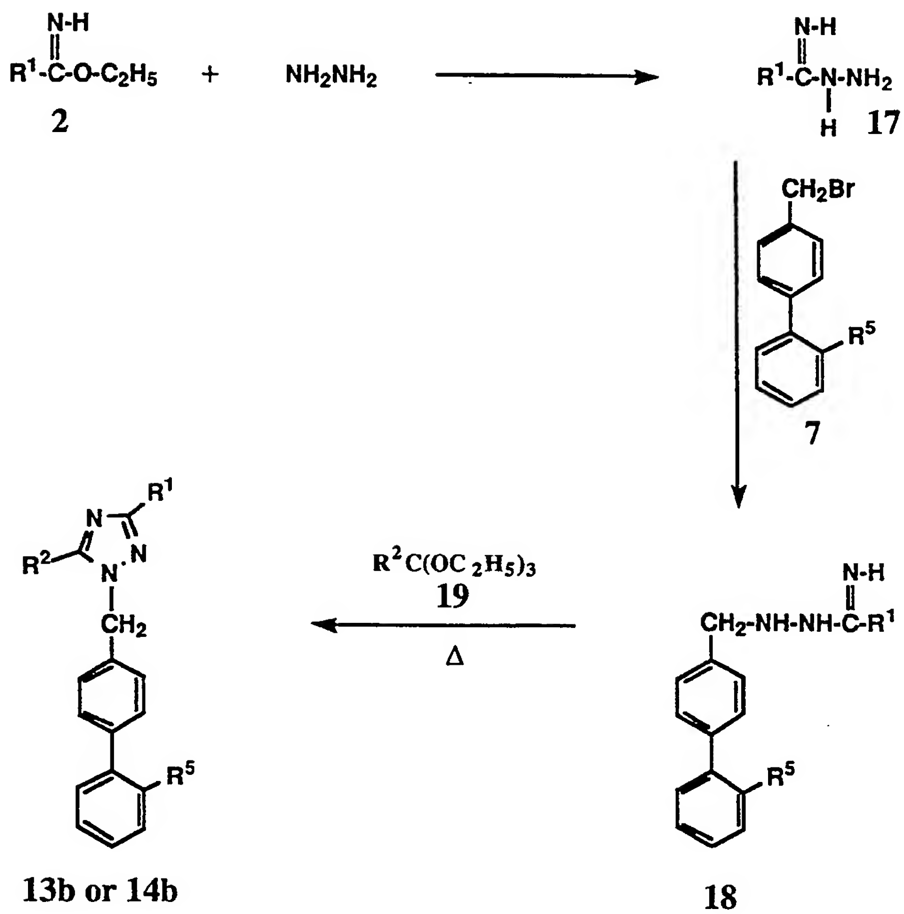
Synthetic Scheme IV shows the coupling reaction of the 1H-1,2,4-triazole 1 with the appropriate alkylating reagent 7. In the first step, 1 is treated with a base, such as sodium hydride, to generate the corresponding anion 11. Anion 11 is reacted with an alkylating agent 7 to give a mixture of regioisomers 12a and 12b. The isomer mixture may be converted to mixtures of the corresponding acids 13a and 13b or tetrazoles 14a and 14b by treatment with the appropriate reagent. Or, the isomers 12a and 12b may be separated by chromatographic methods, and each isomer may be reacted with the appropriate reagent to provide the acid- or tetrazole-substituted end product.

Scheme V


CH2Br
R5
+
O
R2-C-N-NH2
H
7
3
O
R2-C-N-N-CH2
H H
R5
15
N-H
R1-C-OC2H5
2
O
N-H
R2-C-N-N-C-R1
H CH2
R5
16
Δ
R2
N
R1
N
N
CH2
R5
13a or 14a

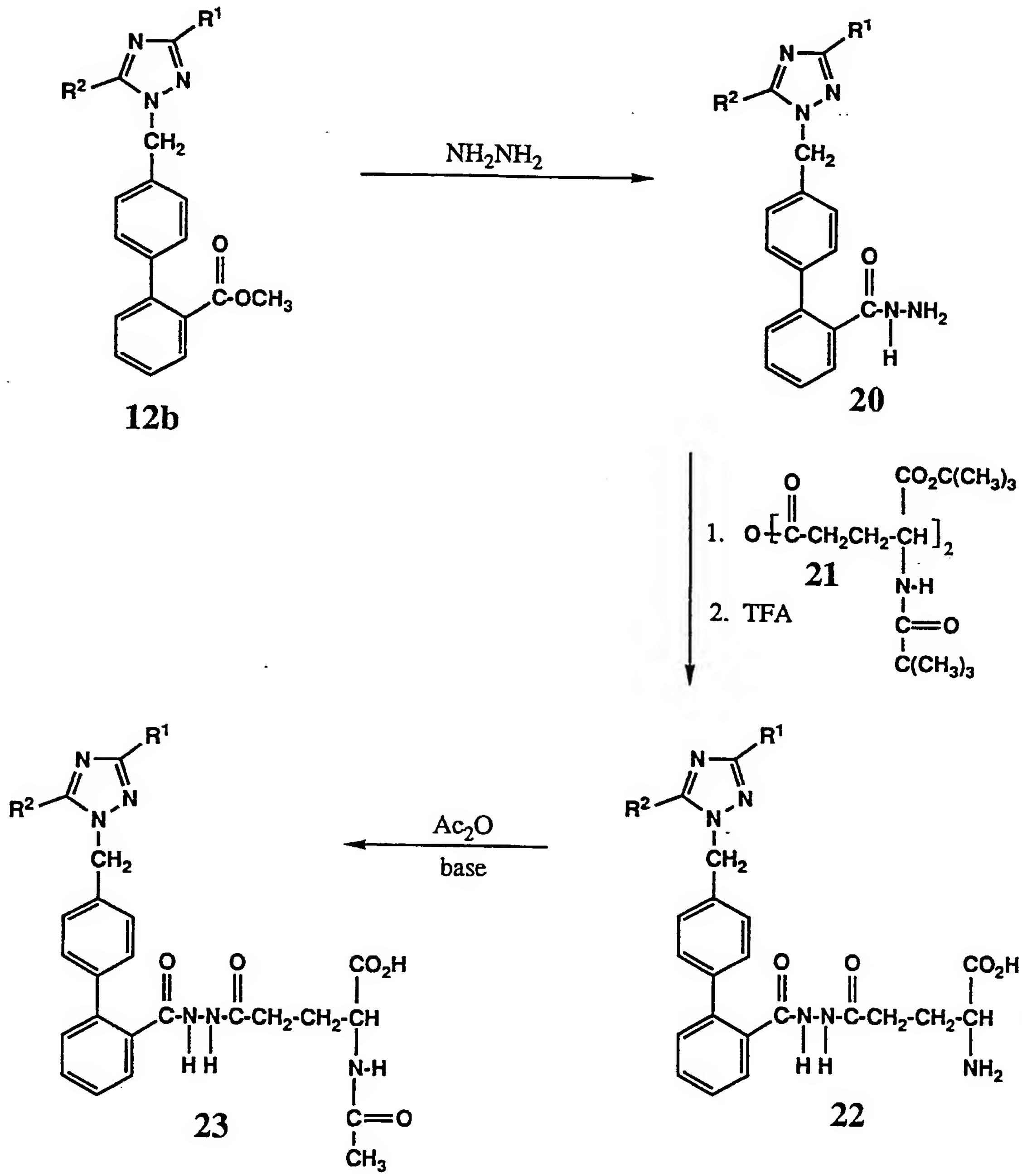
Synthetic Scheme V shows the regioselective synthesis of isomer 13a or 14a from Scheme IV. In the first step of the reaction, an alkylating agent 7 is reacted with an appropriate hydrazide 3 to provide substituted hydrazide 15. An imidate 2 is reacted with hydrazide 15 to provide intermediate 16 which cyclizes upon heating to provide the corresponding product compound 13a or 14a.

Scheme VI


N-H
R1-C-O-C2H5
2
+
NH2NH2
N-H
R1-C-N-NH2
H
17
CH2Br
R5
7
N-H
CH2-NH-NH-C-R1
R5
18
R2C(OC2H5)3
19
Δ
R1
N
N
N
R2
CH2
R5
13b or 14b

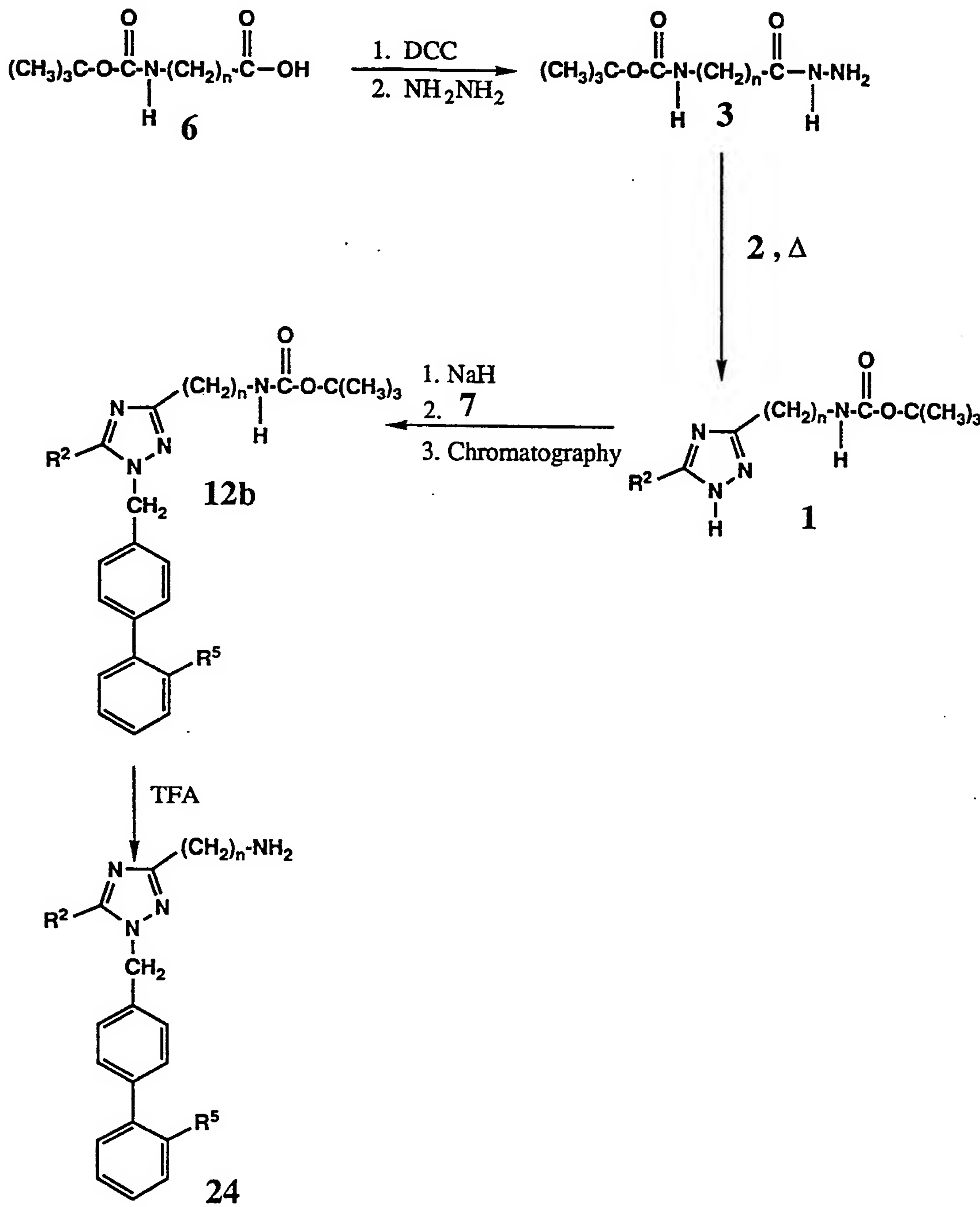
Synthetic Scheme VI shows the regioselective synthesis of isomer 13b or 14b from Scheme IV. In the first step of the reaction, imidate 2 is reacted with hydrazine to give amidazone 17. This intermediate is reacted with alkylating agent 7 to give intermediate 18 which is then cyclized in the presence of heat and an appropriate orthoester 19 to yield the corresponding product compound 13b or 14b.

Scheme VII


R1
R2
N
N
N
CH2
C-OCH3
O
12b
NH2NH2
C-N-NH2
H
20
1. O[C-CH2CH2-CH]2
21
CO2C(CH3)3
N-H
C=O
C(CH3)3
2. TFA
Ac2O
base
C-N-N-C-CH2-CH2-CH
H H
CO2H
N-H
C=O
CH3
23
NH2
22

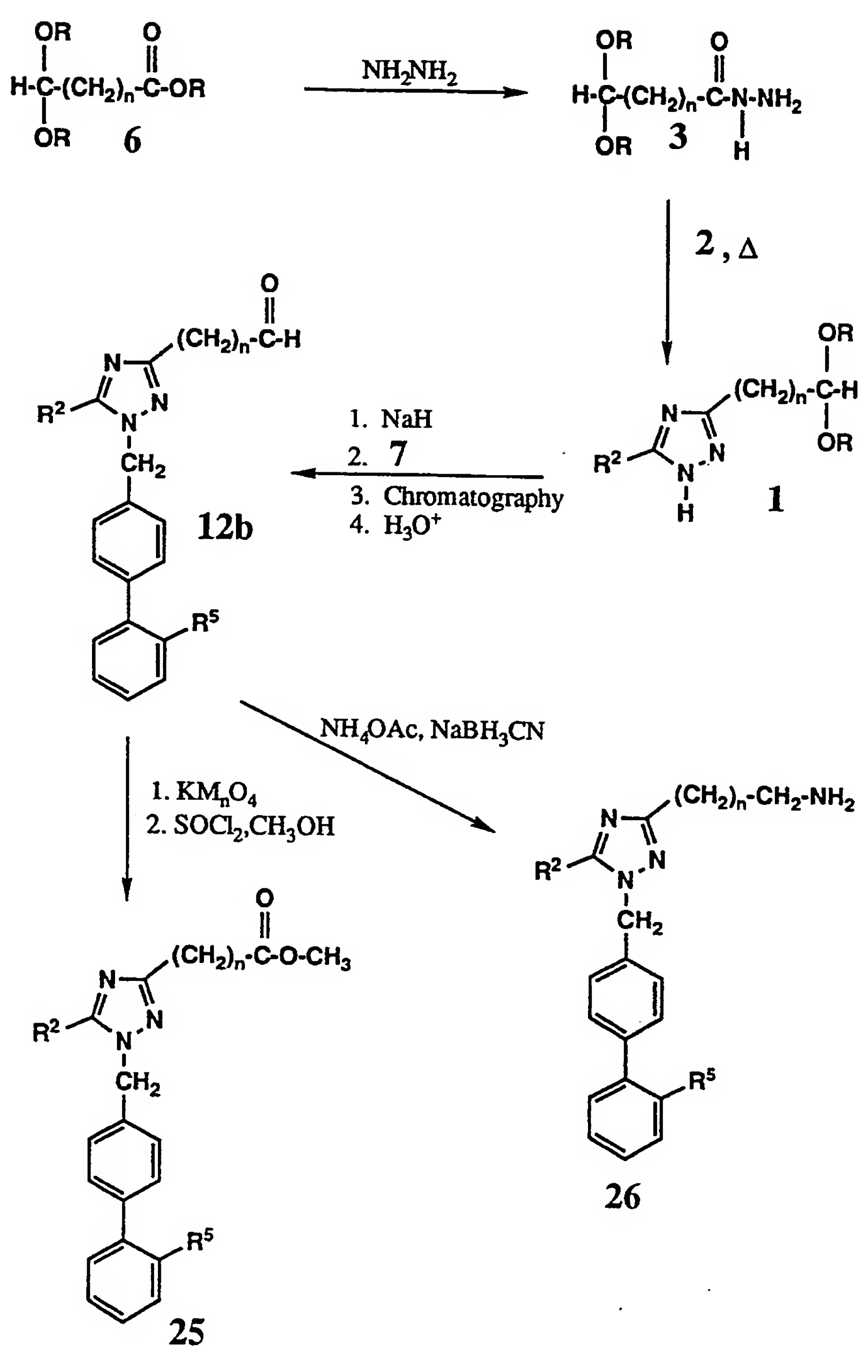
Synthetic Scheme VII shows the preparation of renal-selective angiotensin II antagonists by coupling γ-glutamic acid with an angiotensin II antagonist; the biphenyl R^5 acid moiety of the AII antagonist is coupled to the γ-acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 12b is converted to the hydrazide 20 by the action of hydrazine. In step 2, the hydrazide 20 is first reacted with the symmetrical anhydride of the protected γ-glutamic acid 21 and subsequently reacted with trifluoroacetic acid (TFA) to give the deprotected coupled material 22. In step 3, the free amino group of 22 is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonists 23.

Scheme VIII


(CH3)3C-O-C-N-(CH2)n-C—OH
H 6
1. DCC
2. NH2NH2
(CH3)3C-O-C-N-(CH2)n-C—N-NH2
H 3 H
2 , Δ
(CH2)n-N-C-O-C(CH3)3
R2
H
1
1. NaH
2. 7
3. Chromatography
12b
CH2
R5
TFA
(CH2)n-NH2
24

Synthetic Scheme VIII shows the preparation of angiotensin II antagonists 24 which have an amino moiety incorporated in R^1. In step 1, a protected amino acid 6 is first reacted with dicyclohexylcarbodiimide (DCC) and subsequently reacted with hydrazine to give the hydrazide 3. In step 2, the hydrazide 3 is reacted with the iminoester 2 and subsequently cyclized to the corresponding 1H-1,2,4-triazole 1. In step 3, the anion of 1 is reacted with the appropriate alkylating agent 7 to give a mixture of regioisomers 12a and 12b which can be separated by chromatography. In step 4, the desired isomer 12b is deprotected with TFA to give the free amino AII antagonist 24.

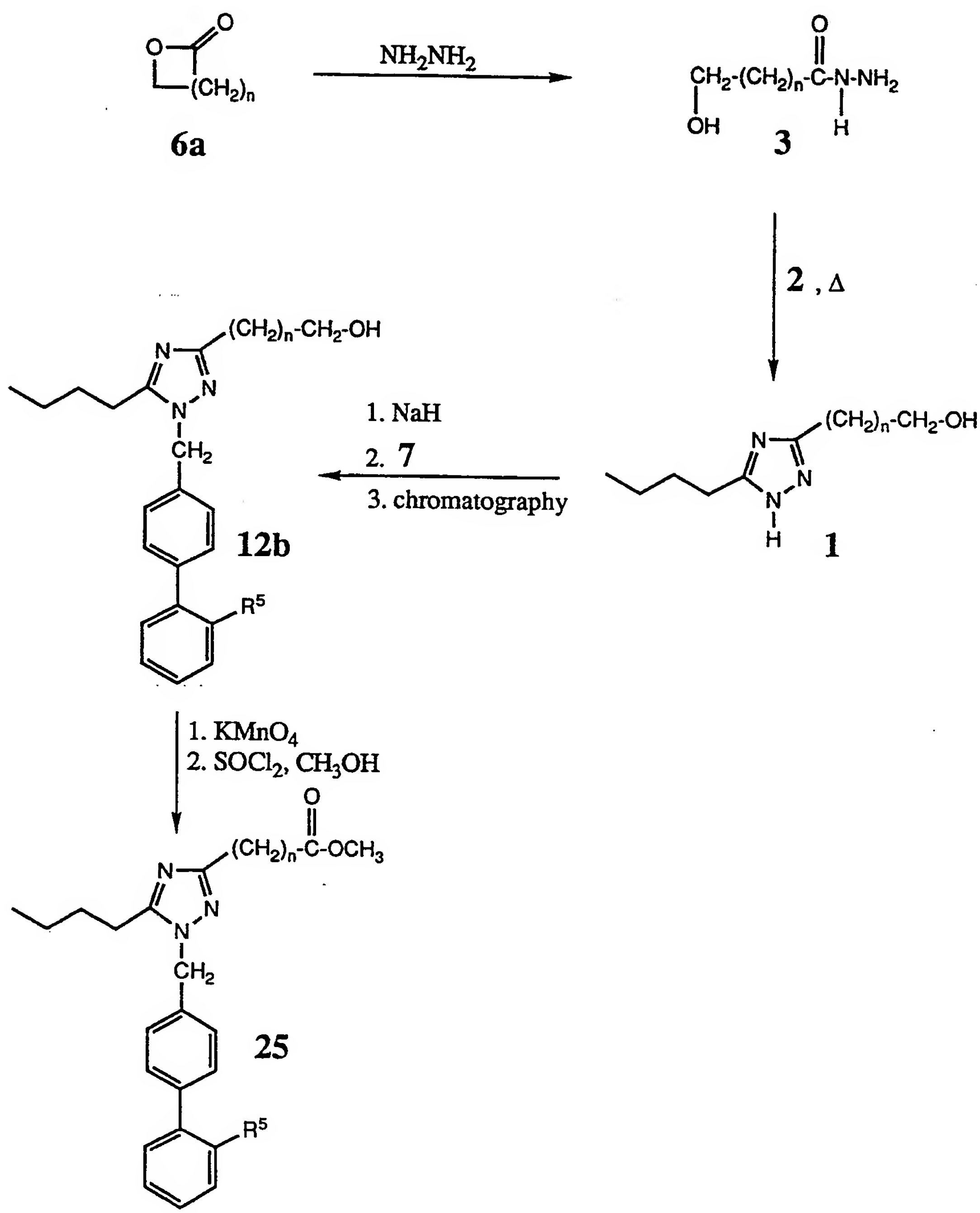
Scheme IX



R = CH_3, C_2H_5

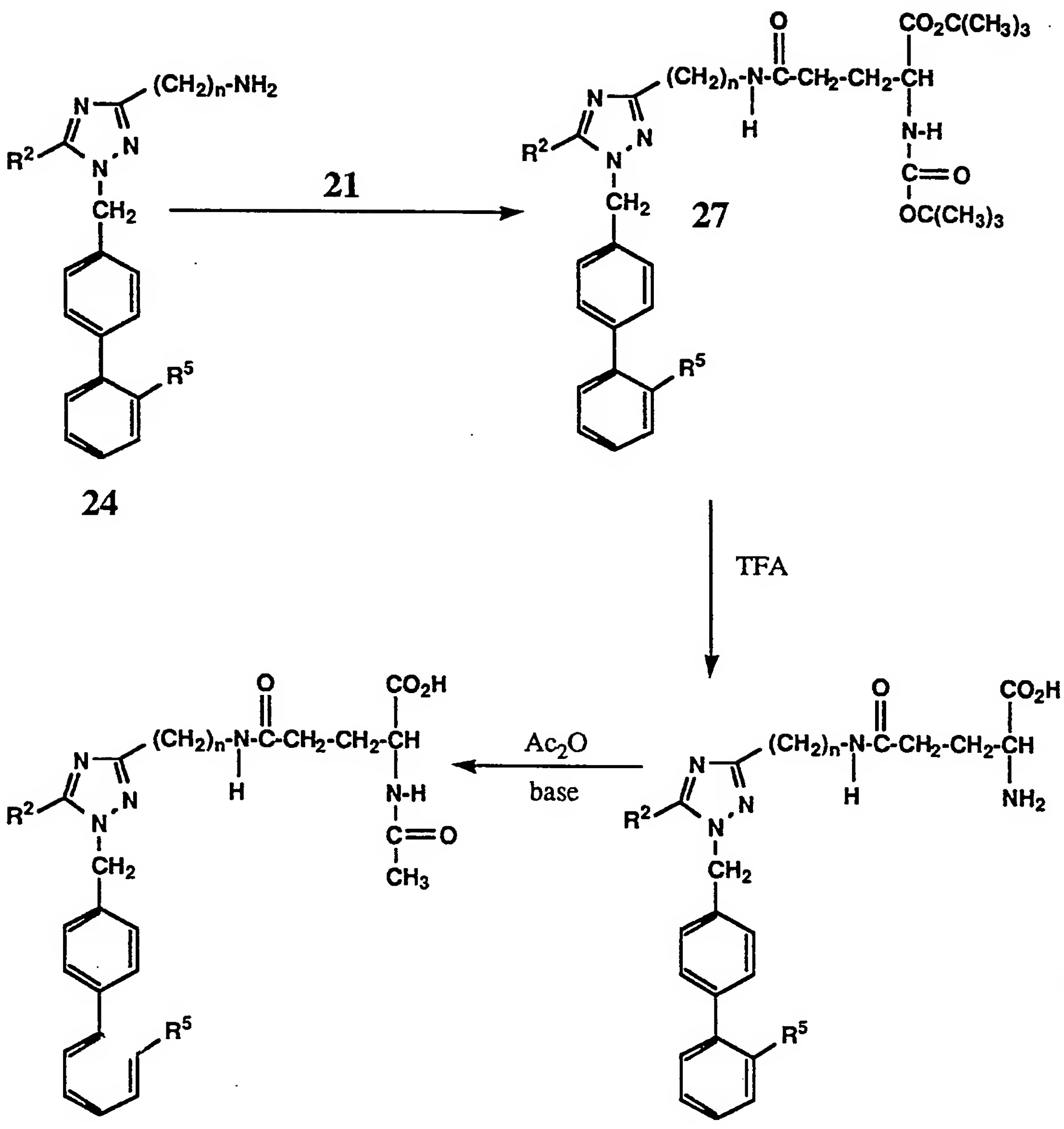
Synthetic Scheme IX shows the preparation of angiotensin II antagonists 25 and 26 which have a carbomethoxy moiety and an amino moiety, respectively, incorporated in R^1. In step 1, the dialkylacetal alkyl ester 6 is reacted with hydrazine to give the hydrazide 3. In step 2, the hydrazide 3 is reacted with the iminoester 2 and subsequently cyclized to the corresponding 1H-1,2,4-triazole 1. In step 3, the anion of 1 is reacted with the apropriate alkylating agent 7 to give a mixture of regioisomers which can be separated by chromatography prior to the generation of the free aldehyde 12b with aqueous acid. In step 4, the aldehyde 12b is oxidized to the corresponding acid with $KMnO_4$ and subsequently converted to the methyl ester 25 by $SOCl_2/CH_3OH$ at -10° or reduced to the corresponding aminomethyl analog 26 (homolog of 24) by $NH_4OAc/NaBH_3CN$.

Scheme X


O
(CH2)n
6a
NH2NH2
O
CH2-(CH2)n-C-N-NH2
OH
H
3
2 , Δ
(CH2)n-CH2-OH
N
N
N
H
1
1. NaH
2. 7
3. chromatography
(CH2)n-CH2-OH
N
N
N
CH2
12b
R5
1. KMnO4
2. SOCl2, CH3OH
O
(CH2)n-C-OCH3
N
N
N
CH2
25
R5

Synthetic Scheme X shows an alternate preparation of angiotensin II antagonists 25 which have a carbomethoxy moiety incorporated in R^1. In step 1, the lactone 6a is reacted with hydrazine to give the hydrazide 3. In step 2, the hydrazide 3 is reacted with the iminoester 2 and subsequently cyclized to the corresponding 1H-1,2,4-triazole 1. In step 3, the anion of 1 is reacted with the appropriate alkylating agent 7 to give a mixture of regioisomers which can be separated by chromatography to give 12b. In step 4, the primary alcohol 12b is oxidized to the corresponding acid with $KMnO_4$ and subsequently converted to the methyl ester 25 by $SOCl_2/CH_3OH$ at -10°.

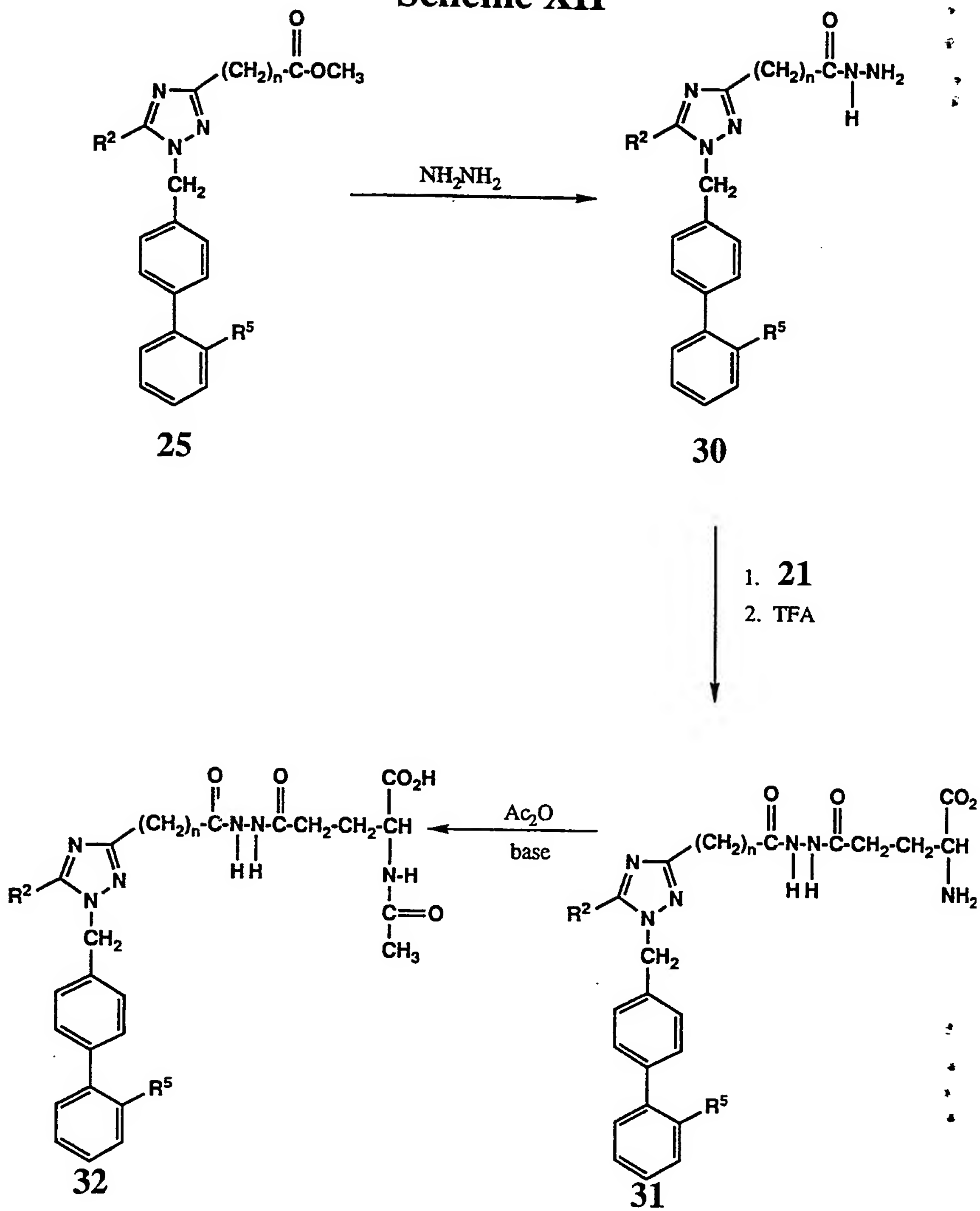
Scheme XI



24 27 28 29

Synthetic Scheme XI shows the preparation of renal-selective angiotensin II antagonists by coupling amino containing AII antagonists 24 with γ-glutamic acid. In step 1, the AII antagonist is reacted with the symmetrical anhydride of the protected γ-glutamic acid 21 to give 27. In step 2, the protected material 27 is reacted with TFA to give the deprotected coupled material 28. In step 3, the free amino compound 28 is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonists 29.

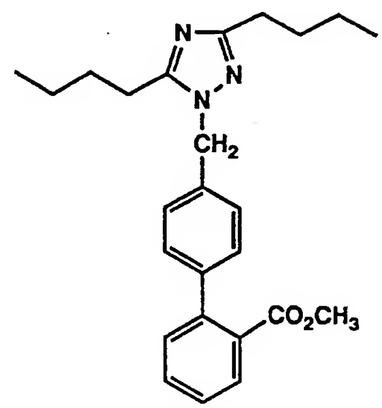
Scheme XII


(CH2)n-C-OCH3
R2
CH2
R5
25
NH2NH2
(CH2)n-C-N-NH2
H
30
1. 21
2. TFA
CO2
(CH2)n-C-N-N-C-CH2-CH2-CH
H H
NH2
31
Ac2O
base
CO2H
N-H
C=O
CH3
32

Synthetic Scheme XII shows the preparation of renal-selective angiotensin II antagonists by coupling γ-glutamic acid with an angiotensin II antagonist; the triazole R^1 acid moiety of the AII antagonist is coupled to the γ-acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 25 is converted to the hydrazide 30 by the action of the hydrazine. In step 2, the hydrazide 30 is first reacted with the symmetrical anhydride of the protected γ-glutamic acid 21 and subsequently reacted with TFA to give the deprotected coupled material 31. In step 3, the free amino group of 31 is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonists 32.

The following Examples 1-78 are detailed descriptions of the methods of preparation of specific angiotensin II antagonist compounds within Formula I. These detailed preparations fall within the scope of, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These Examples #1-#78, as well as methods described in other preparatory examples which follow, are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are given in centigrade degrees, unless otherwise indicated.

Example 1



methyl 4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylate

Step 1: Preparation of 4-bromomethyl-2'-methoxycarbonylbiphenyl.

A 47.46 g (210 mmol) sample of methyl 2-(p-tolyl)benzoate (Chemo Dynamics Inc.) was dissolved in 3L of carbon tetrachloride and treated with 37.33 g (209 mmol) of N-bromosuccinimide (NBS) and 1.17 g (7.13 mmol) of azobisisobutyronitrile (AIBN) at reflux under nitrogen for 24 hours. The reaction mixture was treated again with 1.0 g (6.1 mmol) of AIBN and stirred at reflux for an additional 24 hours. The reaction was filtered and the solvent removed in *in vacuo*. Purification by silica gel chromatography (Waters Prep-500A) using ethyl acetate/hexane (5:95) as eluent provided 50.0 g (78%) of a colorless solid: mp 48-51°C; NMR ($CDCl_3$) δ 3.64 (s, 3H), 4.54 (s, 2H), 7.23-7.63 (m, 7H), 7.81-7.89 (m, 1H). NMR indicated that this material was only 91% pure; it contained 9% of the corresponding dibromocompound (δ 6.70); however, no further attempts at purification were made and this mixture was used in all subsequent alkylation reactions.

Step 2: Preparation of 3,5-dibutyl-1H-1,2,4-triazole.

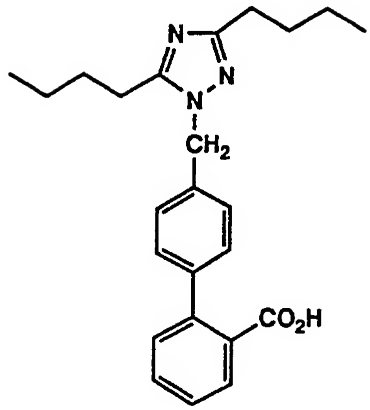
A solution of 64.5 g (0.50 mol) of ethyl iminovalerate [P. Reynaud and R. C. Moreau, Bull. Soc. Chim. France , 2997 (1964)] in 100 mL of methanol was added slowly to 58.0 g (0.50 mol) of valeric acid hydrazide (Lancaster Synthesis) in 400 mL of methanol at 0°C under a nitrogen atmosphere. After the addition was complete, the reaction was allowed to warm to ambient temperature and then stir at reflux for 2 days. The solvent was removed *in vacuo*; purification by silica gel chromatography (Waters Prep-500A) using ethyl acetate/hexane (80:20) gave 78.9 g (93%) of a colorless solid: mp 50.5-51.5°C; NMR ($CDCl_3$) δ 0.88 (t, *J*=7 Hz, 6H), 1.28-1.33 (m, 4H), 1.63-1.77 (m, 4H), 2.72 (t, *J*=7 Hz, 4H); MS (FAB) m/e (rel intensity) 183 (12%), 182 (100), 181 (3), 180 (6), 152 (8), 139 (4); HRMS. Calcd for M+H: 182.1657. Found: 182.1661.

Step 3: Preparation of methyl 4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylate.

Under a static nitrogen atmosphere, 2.01 g (11.0 mmol) of solid 3,5-dibutyl-1H-1,2,4-triazole was added in small portions to 12 mmol of sodium hydride in 50 ml of dimethylformamide (DMF); stirring was continued until hydrogen evolution had ceased. The anion solution was cooled to -10°C (ice/methanol) and treated with a solution of 3.37 g (11.0 mmol) of 4-bromomethyl-2'-methoxycarbonyl-biphenyl in 20 ml of dry DMF. The reaction was allowed to warm to ambient temperature and stir overnight. Methanol (10 ml) was added to destroy any unreacted sodium hydride and the DMF was removed in vacuo. The residue was dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$). Silica gel chromatography (Waters Prep-500A) using 40% ethyl acetate/hexane gave 2.0 g (41%) of compound as an oil: NMR ($CDCl_3$) δ 0.90 (t, *J* = 7 HZ, 3H), 0.94 (t, *J* = 7 Hz, 3H), 1.28-1.47 (m, 4H), 1.62-1.80 (m, 4H), 2.63-

2.75 (m, 4H), 3.63 (s, 3H), 5.27 (s, 2H), 7.13-7.18 (m, 2H), 7.25-7.35 (m, 3H), 7.37-7.44 (m, 1H), 7.48-7.55 (m, 1H), 7.80-7.85 (m, 1H).

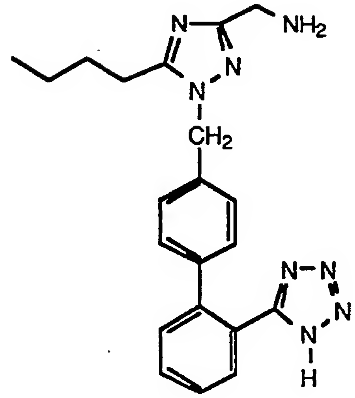
Example 2



4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid

A 2.0 g (4.9 mmol) sample of the methyl ester product compound from Example 1 was dissolved in 80 ml of ethanol and treated with 80 ml of 10% NaOH at ambient temperature for 3 days. The ethanol was removed *in vacuo* and the aqueous phase acidified to pH 1 with hydrochloric acid which caused the product to precipitate; filtration and drying *in vacuo* gave 1.65 g (86%) of colorless compound: mp 134-135°C; NMR (DMSO-d_6) δ 0.85 (t, *J* = 7 Hz, 3H), 0.90 (t, *J* = 7 Hz, 3H), 1.23-1.39 (m, 4H), 1.53-1.68 (m, 4H), 2.59 (t, *J* = 7 Hz, 2H), 2.78 (t, *J* = 7 Hz, 2H), 5.37 (s, 2H), 5.37 (s, 2H), 7.18-7.26 (m, 2H), 7.28-7.37 (m, 3H), 7.42-7.48 (m, 1H), 7.53-7.60 (m, 1H), 7.70-7.75 (m, 1H).

Example 3



5-[4'-[(3-aminomethyl-5-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Step 1: Preparation of N-Triphenylmethyl-5-[2-(4'-bromomethylbiphen-2-yl]tetrazole.

A 542.5 g (2.4 mol) sample of methyl 2-(p-tolyl)benzoate (Chemo Dynamics Inc.) was dissolved in 5.5 L of ethanol and treated with 3 L (7.5 mol) of 2.5 N sodium hydroxide. The reaction was stirred overnight at ambient temperature and treated with an additional 480 ml (6.0 mol) of sodium hydroxide; stirring was continued for an additional 24 h and the ethanol removed *in vacuo*. The remaining solution was cooled in ice and acidified to pH 1 with hydrochloric acid which caused the product to precipitate; filtration and drying *in vacuo* gave 510 g (100%) of crude 2-(p-tolyl)benzoic acid: mp 145.0-147.5°C; NMR ($CDCl_3$) δ 2.40 (s, 3H), 7.17-7.28 (m, 4H), 7.35-7.45 (m, 2H), 7.51-7.59 (m, 1H), 7.90-7.97 (m, 1H). The crude acid was suspended in 1 L of toluene and slowly treated with 400 g (3.15 mol) of oxalyl chloride under nitrogen. The reaction was allowed to stir at ambient temperature for 4.5 h and concentrated *in vacuo* to remove excess oxalyl chloride. The residue was redissolved in 2L of toluene and treated with 92.8 g (5.46 mol) of anhydrous ammonia. The

reaction was filtered and the filtrate concentrated *in vacuo* producing 424 g (84%) of crude 2-(p-tolyl)benzamide: mp 128-130°C; NMR ($CDCl_3$) δ 2.40 (s, 3H), 5.28 (br s, 1H), 5.77 (br s, 1H), 7.21-7.53 (m, 7H), 7.76-7.83 (m, 1H). The crude amide was treated with 1420 ml (19.5 mol) of thionyl chloride at reflux for 3.5 h. The reaction was filtered and the thionyl chloride removed *in vacuo*. The residue was dissolved in 800 ml of toluene and reconcentrated *in vacuo*. On standing overnight, the residue crystallized. The crystals were collected and washed with hexane to give 296 g (64%) of 2-(p-tolyl)benzonitrile: mp 50.5-52.0°C; NMR ($CDCl_3$) δ 2.42 (s, 3H), 7.22-7.34 (m, 2H), 7.37-7.52 (m, 3H), 7.58-7.66 (m, 1H), 7.72-7.78 (m, 1H). A 286 g (1.48 mol) sample of the crude nitrile was dissolved in 1630 mL to toluene and treated with 377 g (1.8 mol) of trimethyltinazide at reflux for 24 h. The reaction was cooled; filtration gave 600 g of crude N-trimethylstannyl-5-[2-(4'-methylbiphen-2-yl]tetrazole: mp 271-272°C (dec.); NMR (DMSO-d_6) δ 0.36 (br t, *J*=34 Hz, 9H), 2.24 (s, 3H), 6.89-7.06 (m, 4H), 7.35-7.55 (m, 4H). The crude N-trimethylstannyl tetrazole was suspended in 4270 mL of toluene and 287 mL of anhydrous tetrahydrofuran (THF) and treated with 63.4 g (173 mol) of anhydrous hydrogen chloride at ambient temperature under nitrogen with stirring. The reaction was allowed to stand overnight and filtered; recrystallization from toluene gave 217 g (62%) of 5-[2-(4'methylbiphen-2-yl)]tetrazole as a solid: mp 149-152°C; NMR (DMSO-d_6) δ 2.28 (s, 3H), 6.94-7.02 (m, 2H), 7.08-7.15 (m, 2H), 7.50-7.59 (m, 2H), 7.62-7.72 (m, 2H). A 200 g (0.85 mol) sample of the tetrazole was suspended in 3.3 L of dichloromethane and treated with 262 g (0.91 mol) of triphenylmethyl chloride and 141 mL (1.0 mol) of anhydrous triethylamine. The reaction was stirred at reflux for 3 h under nitrogen, washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. Recrystallization gave 338 g (83%) of N-triphenylmethyl-5-[2-(4'-methylbiphen-2-yl)]tetrazole as a colorless solid: mp 170-173°C; NMR ($CDCl_3$) δ 2.27 (s, 3H), 6.86-6.96 (m, 8H), 6.98-7.04 (m,

2H), 7.09-7.52 (m, 12H), 7.86-7.94 (m, 1H). The N-triphenylmethyl tetrazole was dissolved in 4260 mL of carbon tetrachloride and treated with 126.4 g (0.71 mol) of N-bromosuccinimide (NBS) and 11.9 g (49 mmol) of benzoyl peroxide at reflux for 3.5 h. The reaction was filtered and the solvent removed <u>in vacuo</u>. Recrystallization from toluene gave 277 g (59%) of N-triphenylmethyl-5-[2-(4'-bromor thylbiphen-2-yl)]tetrazole as a colorless solid: mp 140-1 C; NMR ($CDCl_3$) δ 4.39 (s, 2H), 6.85-6.95 (m, 7H), 7.06-7.15 (m, 4H), 7.22-7.43 (m, 9H), 7.45-7.55 (m, 2H), 7.94-8.01 (m, 1H). NMR indicated that this material was only 85% pure; it contained 7% of corresponding dibromo-compound (δ 6.50) and 8% of starting material (δ 2.27); however, no further attempts at purification were made and this mixture was used in all subsequent alkylation reactions.

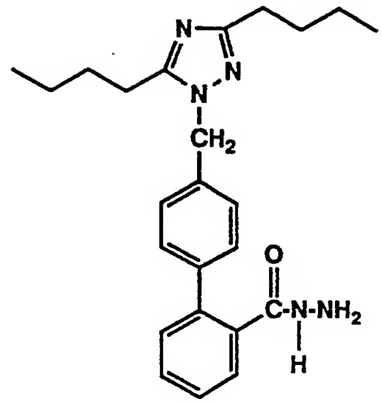
<u>Step 2</u>: <u>Preparation of 5-butyl-3-tert-butoxycarbonylamino-methyl-1H-1,2,4-triazole</u>.

Under nitrogen, a colution of 5.0 g (15.6 mmol) of anhydrous hydrazine in 100 mL of methanol is cooled to 0°C and treated with a solution of 25.0 g (13.2 mmol) of N-BOC glycine methyl ester (Chemical Dynamics Corporation) in 50 mL of methanol. The reaction is allowed to warm to ambient temperature and stirred overnight. Concentration <u>in vacuo</u> gives the crude hydrazide which is purified either by recrystallization or by silica gel chromatography (Waters Prep-500A). A 18.9 g (100 mol) sample of hydrazide is dissolved in 100 mL of methanol and is treated with 12.9 g (100 mmol) of ethyl iminovalerate under nitrogen. The reaction is stirred at reflux overnight and concentrated <u>in vacuo</u>. Purification by silica gel chromatography (Waters Prep-500A) gives 5-butyl-3-tert-butoxycarbonylaminomethyl-1<u>H</u>-1,2,4-triazole.

Step 3: Preparation of 5-[4'-[(3-aminomethyl-5-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

Under a static nitrogen atmosphere, 3.81 g (15.0 mmol) of 3-butyl-5-tert-butoxycarbonylamino-1H-1,2,4-triazole is added slowly to 15 mmol of sodium hydride in 50 ml of dimethylformamide (DMF); stirring is continued until hydrogen evolution has ceased. The anion solution is cooled to -10°C (ice/methanol) and treated with a solution of 8.45 g (15.0 mmol) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-2-yl)]tetrazole in 20 ml of dry DMF. The reaction is allowed to warm to ambient temperature and stir overnight. Methanol (10 ml) is added to destroy any unreacted sodium hydride and the DMF is removed *in vacuo*. The residue is dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$). Purification by silica gel chromatography gives the desired isomer which is dissolved in 100 mL of TFA and is stored at ambient temperature overnight. The reaction is cooled to 0°C, 50 mL of water is added, and is allowed to stir at ambient temperature overnight. The solvent is removed *in vacuo* and the residue is dissolved in acetonitrile/water. Purification by reverse phase chromatography (Waters Delta Prep.-3000) provides pure 5-[4'-[(3-aminomethyl-5-butyl-1H-1,2,4-triazol-1-yl][1,1'-biphenyl]-2-yl]-1H-tetrazole as the TFA salt.

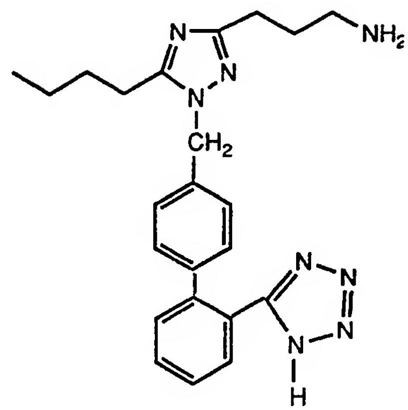
Example 4



4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid, hydrazide

A 7.10 g (17.5 mmol) sample of the methyl ester product compound of Example 1 was dissolved in 150 ml of methanol and treated with 22 ml (22.2 g 695 mmol) of anhydrous hydrazine under a static nitrogen atmosphere. The reaction was stirred at reflux for 2 days and concentrated *in vacuo* to give 7.03 g (99%) of compound which was a colorless glass: NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 0.94 (t, J = 7 Hz, 3H), 1.28-1.47 (m, 4H), 1.62-1.78 (m, 4H), 2.62-2.73 (m, 4H), 3.5-4.1 (br s, 2H), 5.26 (s, 2H), 6.53 (s, 1H), 7.13-7.63 (m, 8H).

Example 5



5-[4'-[[3-(3-aminopropyl)-5-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

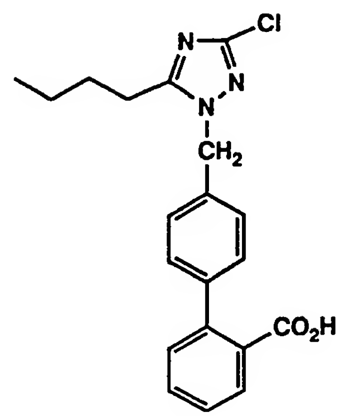
Step 1: Preparation of 5-butyl-3-(3-tertbutoxy-carbonylaminoprioyl)-1H-1,2,4-triazole

Under nitrogen, 60.0 g (0.30 mol) of N-BOC-γ-aminobutyric acid (BACHEM) is dissolved in 1200 mL of methylene chloride and treated with 30.5 g (0.15 mol) of dicyclohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 hours and filtered under nitrogen. The anhydride solution is then added to a solution of 1.58 g (98.5 mmol) of anhydrous hydrazine in 100 mL of methylene chloride at 0°C. The reaction is allowed to warm to ambient temperature and stirred overnight. Concentration *in vacuo* gives the crude hydrazide which is purified either by recrystallization or by silica gel chromatography (Waters Prep-500A). A 21.7 g (100 mmol) sample of hydrazide is dissolved in 100 mL of methanol and treated with 12.9 g (100 mmol) of ethyl iminovalerate under nitrogen. The reaction is stirred at reflux overnight and concentrated *in invacuo*. Purification by silica gel chromatography (Waters Prep-500A) gives 5-butyl-3-(3-tert-butoxycarbonylaminopropyl-1*H*-1,2,4-triazole.

Step 2: Preparation of 5-[4'-[[3-(3-aminopropyl)-5-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Under a static nitrogen atmosphere, 14.4 g (46.0 mmol) of 3-(3-N-BOC-aminopropyl)-5-butyl-1H-1,2,4-triazole is added in small portions to 50 mmol of sodium hydride in 250 ml of dimethylformamide (DMF); stirring is continued until hydrogen evolution has ceased. The anion solution is cooled to -10°C (ice/methanol) and is treated with a solution of 25.5 g (46.0 mmol) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-2-yl)]tetrazole (from Step 1 of Example 3) in 100 ml of dry DMF. The reaction is allowed to warm to ambient temperature and stir overnight. Methanol (10 ml) is added to destroy any unreacted sodium hydride and the DMF is removed in vacuo; the residue is dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$). Purification by silica gel chromatography gives the desired isomer which is dissolved in 200 mL of TFA and is stirred at ambient temperature overnight. The reaction is cooled to 0°C, 100 mL of water is added, and is allowed to stir at ambient temperature overnight. The solvent is removed in vacuo and the residue is dissolved in acetonitrile/water. Purification by reverse phase chromatography (Waters Delta Prep-3000) provided pure 5-[4'-[[3-(3-aminopropyl)-5-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as the TFA salt.

Example 6



4'-[(5-butyl-3-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid

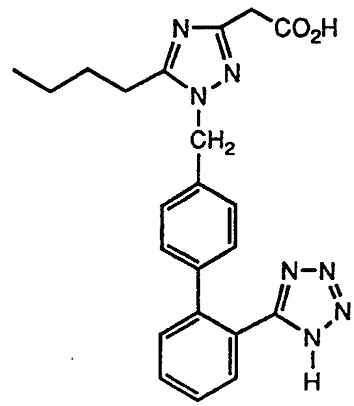
Step 1: Preparation of 3-butyl-5-chloro-1H-1,2,4-triazole.

A 10.0 g (80 mmol) sample of 3-butyl-1H-1,2,4-triazole [H. Paul, G. Hilgetag, and G. Jahnchen, Chem. Ber., 101, 2033 (1968)] was dissolved in 320 mL of water containing 7.0 g (177 mmol) of sodium hydroxide. With stirring, the solution was cooled to 0°C and chlorine was introduced over 3 h. The reaction was purged with nitrogen overnight and the solution extracted with chloroform. The extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give 16.8 g of a colorless oil which was placed in 200 mL of water and treated twice with 8.0 g (80 mmol) of sodium metabisulfite. The pH of the reaction medium was adjusted to 6 with 1M sodium carbonate prior to extraction with chloroform; the extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give 14.9 g of crude product. Purification by silica gel chromatograph (Waters Prep-500A) using chloroform/methanol (95:5) gave 9.53 g (75%) of a colorless solid: mp 104-105°C; NMR ($CDCl_3$) δ 0.94 (t, *J*=7 Hz, 3H), 1.33-1.47 (m, 2H), 1.68-1.83 (m, 2H), 2.80 (t, *J*=7 Hz, 2H); MS (FAB) m/e (rel intensity) 162 (28), 160 (100), 158 (10), 130 (5), 126 (10), 117 (5); HRMS. Calcd for M+H: 160.0642. Found: 160.0651.

Step 2: Preparation of 4'-[(5-butyl-3-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid.

Under a static nitrogen atmosphere, 5.0 g (31.3 mmol) of solid 5-butyl-3-chloro-1H-1,2,4-triazole was added in small portions to 32 mmol of sodium hydride in 50 ml of dimethylformamide (DMF); stirring was continued until hydrogen evolution had ceased. The anion solution was cooled to -10°C (ice/methanol) and treated with a solution of 9.55 g (31.3 mmol) of 4-bromomethyl-2'-methoxycarbonylbiphenyl in 20 ml of dry DMF. The reaction was allowed to warm to ambient temperature and stir overnight. Methanol (10 ml) was added to destroy any unreacted sodium hydride and the DMF was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$) to give 12.2 g of crude material was obtained which was a clear golden oil. A 4.81 g sample of this material was dissolved in 250 ml of methanol and treated with 250 ml of 10% NaOH at ambient temperature for 2 days. A portion of the isomer mixture of acids was separated by reverse phase chromatography (Waters Delta Prep-3000) using isocratic 45% acetronitrile/water (0.05% TFA). The faster moving isomer (250 mg) was identified as the 3-chloro isomer: NMR (DMSO-d_6) δ 0.86 (t, *J* = 7 Hz, 3H), 1.23-1.36 (m, *J* = 7 Hz, 2H), 1.54-1.65 (m, *J* = 7 Hz, 1H), 2.80 (t, *J* = 7Hz, 2H), 5.40 (s, 2H), 7.23-7.58 (m, 7H), 7.72-7.77 9m, 1H).

Example 7



5-[4'-[(5-butyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Step 1: Preparation of 5-butyl-3-(2,2-diethoxyethyl)-1H-1,2,4-triazole.

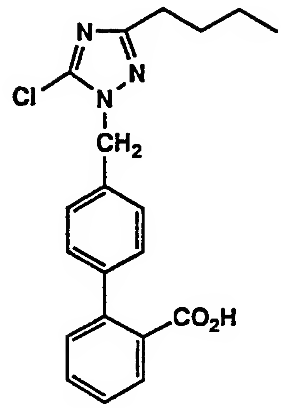
Under nitrogen, a solution of 38.4 g (1.2 mol) of anhydrous hydrazine in 500 mL of methanol is cooled to 0°C and treated with a solution of 190.0 g (1.0 mol) of ethyl 3,3-diethoxypropionate (Aldrich) in 200 mL o fmethanol. The reaction is allowed to warm to ambient temperature and is stirred overnight at reflux. Concentration in vacuo gives the crude hydrazide which is purified either by recrystallization or by silica gel chromatography (Waters Prep-500A). A 17.6 g (100 mmol) sample of hydrazide is dissolved in 100 mL of methanol and is treated with 12.9 g (100 mmol) of ethyl iminovalerate under nitrogen. The reaction is stirred at reflux overnight and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500A) gives 5-butyl-3-(2,2-di-ethoxyethyl)-1H-1,2,4-triazole.

Step 2: Preparation of 5-[4'-[(5-butyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl) methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

Under a static nitrogen atmosphere, 11.1 g (46.0 mmol) of 5-butyl-3-(2,2-diethoxyethyl)-1H-1,2,4-triazole is added in small portions to 50 mmol of sodium hydride in 250 ml of dimethylformamide (DMF); stirring is continued until hydrogen evolution has ceased. The anion solution is cooled to -10°C (ice/methanol) and is treated with a solution of 25.5 g (9.2 mmol) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-2-yl)]tetrazole (from Step 1 of Example 3) in 100 ml of dry DMF. The reaction is allowed to warm to ambient temperature and stir overnight. Methanol (10 ml) is added to destroy any unreacted sodium hydride and the DMF is removed _in vacuo_; the residue is dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$). Purification by silica gel chromatography gives the desired isomer which is treated with 3N HCl/methanol (1:1) at reflux for 4 hours. The methanol is removed _in vacuo_ and the pH is adjusted to 9 with NaOH. The solution is extracted with ethyl acetate twice to remove triphenylmethanol. The pH is readjusted to 3 with 6N HCl and the solution is extracted 3 times with ethyl acetate, the extracts are combined, washed with water, and dried ($MgSO_4$). Concentration _in vacuo_ gives 5-[4'-[(5-butyl-3-formalmethyl-1H-1,2,4-triazole-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole. A 4.01 g (10.0 mmol) sample of the free aldehyde is dissolved in 500 mL of acetone/water (1:1) and is treated with 1.65 g (10.4 mmol) of solid $KMnO_4$ over 6 hours at ambient temperature. The reaction is allowed to stir overnight and excess $KMnO_4$ is destroyed by the addition of 100 mL of methanol. The reaction is filtered and the acetone is removed _in vacuo_; the pH is adjusted to 3 with 6N HCl and the product is extracted with ethyl acetate. The extracts are combined, washed with water, and dried ($MgSO_4$). Concentration _in vacuo_ gives the crude product which was dissolved in acetonitrile/water;

purification by reverse phase chromatograpphy (Waters Delta Prep-3000) provides pure 5-[4'-[5-butyl-3-caroxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1-biphenyl]-2-yl]-1H-tetrazole.

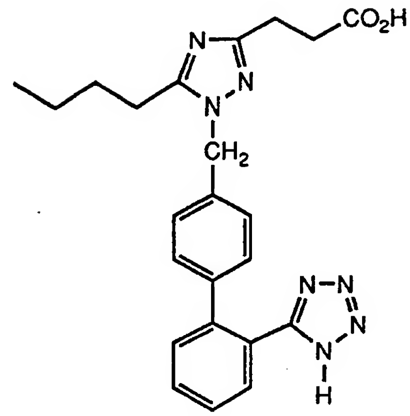
Example 8



4'-[(3-butyl-5-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid

The slower moving isomer (120 mg) isolated in Example 6 was identified as the 5-chloro isomer: NMR (DMSO-d_6) δ 0.88 (t, *J* = 7 Hz, 3H), 1.25-1.35 (m, *J* = 7 Hz, 2H), 1.56-1.67 (m, *J* = 7 Hz, 2H), 2.49 (t, *J* = 7 Hz, 2H), 5.37 (s, 2H), 7.23-7.58 (m, 7H), 7.72-7.77 (m, 1H).

Example 9



5-[4'-[[5-butyl-3-(2-carboxyethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Step 1: Preparation of 5-butyl-3-(3-hydroxypropyl)-1H-1,2,4-triazole.

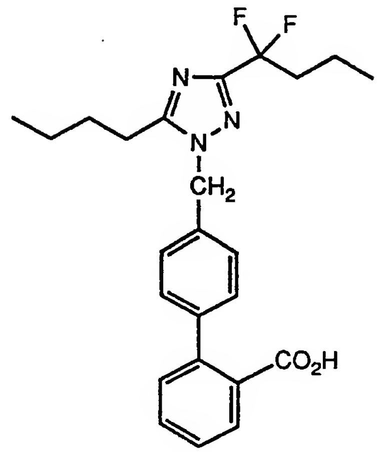
Under nitrogen, a solution 38.4 g (1.2 mol) of anhydrous hydrazine in 500 mL of methano is cooled to 0°C and is treated with a solution of 86.0 g (1.0 mol) of γ-butyrolactone (Aldrich) in 100 mL of methanol. The reaction is allowed to warm to ambient temperature and stir overnight at reflux. Concentration in vacuo gives the crude hydrazide which is purified either by recrystallization or by silica gel chromatography (Waters Prep-500A). A 11.8 g (100 mmol) sample of hydrazide is dissolved in 100 mL of methanol and is treated with 12.9 g (100 mmol) of ethyl iminovalerate under nitrogen. The reaction is stirred at reflux overnight and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500A) gives 5-butyl-3-(3-hydroxypropyl)-1H-1,2,4-triazole.

Step 2: Preparation of 5-[4'-[[5-butyl-3-(2-carboxyethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

Under a static nitrogen atmosphere, 8.4 g (46 mmol) of 5-butyl-3-(3-hydroxypropyl)-1H-1,2,4-triazole is added in small portions to 50 mol of sodium hydride in 250 ml of dimethylformamide (DMF); stirring is continued until hydrogen evolution has ceased. The anion solution is cooled to -10°C (ice/methanol) and treated with a solution of 25.5 g (46 mmol) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-2-yl)]tetrazole (from Step 1 of Example 3) in 100 ml of dry DMF. The reaction is allowed to warm to ambient temperature and stir overnight. Methanol (10 ml) is added to destroy any unreacted sodium hydride and the DMF is removed in vacuo; the residue is dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$). Purification by silica gel chromatography gives a mixture of isomers which is treated with 3N HCl/methanol (1:1) at reflux for 4 hours. The methanol is removed in vacuo and the pH is adjusted to 9 with NaOH. The solution is extracted with ethyl acetate twice to remove triphenylmethanol. The pH is readjusted to 3 with 6 N HCl and the solution is extracted 3 times with ethyl acetate; the extracts are combined, washed with water, and dried ($MgSO_4$). Concentration in vacuo gives a mixture of 5-butyl-3-(3-hydroxypropyl)- and 3-butyl-5-(3-hydroxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole isomers. A 4.17 g (10.0 mmol) sample of the isomeric mixture of alcohols is dissolved in 500 mL of acetone/water (1:1) and is treated with 3.30 g (20.8 mmol) of solid $KMnO_4$ over 6 hours at ambient temperature. The reaction is allowed to stir overnight and excess $KMnO_4$ is destroyed by the addition of 100 mL of methanol. The reaction is filtered and the acetone is removed in vacuo; the pH is adjusted to 3 with 6N HCl and the product is extracted with ethyl acetate. The extracts are combined, washed with water, and dried ($MgSO_4$). Concentration in

vacuo give sthe isomeric mixture of acids; purification by reverse phase chromatography (Waters Delta Prep-3000) provides pure 5-[4'-[[5-butyl-3-(2-carboxyethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

Example 10



5-[4'-[[5-butyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid

Step 1: Preparation of 3-butyl-5-(1,1-difluorobutyl)-1H-1,2,4-triazole.

Under nitrogen, a stirred solution of 56.9 g (0.65 mol) of N-tert-butyl-N-methylamine (Fluka) and 66.1 g (0.65 mol) of triethylamine in 1 L of methylene chloride was cooled to 0°C and treated with neat difluoroacetic anhydride [E. Sawicki, J. Org. Chem., 21, 376 (1956)] at such a rate as to maintain the reaction temperature below 10°C. The reaction was allowed to warm to ambient temperature and stir overnight. All volitiles were removed in vacuo (bath temperature < 35°C) and the residue redissolved in methylene chloride; the solution was washed with saturated sodium bicarbonate, dried ($MgSO_4$), and concentrated to give 94 g (89%) of a yellow liquid. Vacuum distillation gave 86 g (81%) of colorless N-tert-butyl-N-methyldifluoroacetamide: bp 87-88°C (22 mm); ^1H NMR ($CDCl_3$) δ 1.37 (s, 9H), 2.93 (t, J=3 Hz, 3H), 5.97 (t, J=57 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ -122.20 (d, J=57 Hz, 2F). A 17.0 g (103 mmol) sample of the amide was dissolved in 50 mL of dry THF and added slowly to a solution of 145 mmol of

lithium diisopropylamine (LDA) in 450 mL of dry THF at -78°C. The reaction was allowed to stir for 1 h at -78°C prior to the addition of 17 mL (175 mmol) of 1-iodopropane by syringe. Stirring at -78°C was continued for 1 hr and then the reaction was allowed to warm to ambient temperature overnight. Methanol (10 mL) was added and the reaction was concentrated in vacuo; the residue was dissolved in methylene chloride and washed with 1N hydrochloric acid, dried ($MgSO_4$) and reconcentrated to give 17.6 g (83%) of crude product. Purification by vacuum distillation gave 13.3 g (62%) of colorless N-tert-butyl-N-methyl-2,2-difluoro-valeramide: bp 125-130°C (84 mm); 'H NMR ($CDCl_3$) δ 0.94 (t, *J*=7 Hz, 3H), 1.37 (s, 9H), 1.40-1.52 (m, 2H), 1.95-2.15 (m, 2H); ^{19}F NMR ($CDCl_3$) δ -100.29 (t, *J* = 20Hz, 2F). The difluorovaleramide was dissolved in 30 mL of trifluoroacetic acid (TFA) and stirred at reflux overnight under nitrogen. The solvent was removed in vacuo and the residue dissolved in methylene chloride; the solution was washed with water, dried ($MgSO_4$) and concentrated to give 9.7 g (100%) of crude N-methyl-2,2-difluorovaleramide: 'H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7 Hz, 3H), 1.36-1.51 (m, 2H), 1.90-2.11 (m, 2H), 2.84 (d, *J* = 6 Hz, 3H), 6.60-6.85 (br s, 1H); ^{19}F NMR ($CDCl_3$) δ -106.98 (t, *J* = 19 Hz, 2F). The crude N-methyl amide was dissolved in 40 mL of 6N hydrochloric acid and stirred at reflux for 24 hr. The reaction was cooled to ambient temperature and extracted with methylene chloride; the extracts were combined, dried ($MgSO_4$), and concentrated to give 8.0 g (56%) of crude 2,2-difluorovaleric acid: 'H NMR ($CDCl_3$) δ 1.00 (t, *J* = 7 Hz, 3H), 1.46-1.63 (m, 2H), 1.97-2.17 (m, 2H); ^{19}F NMR ($CDCl_3$) δ -107.16 (t, *J* = 18 Hz, 2F). A 4.83 g (35 mmol) sample of the crude acid was dissolved in 25 mL (35.2 g, 174 mmol) of phthaloyl chloride in a flask equipped with a reflux condenser and stirred under nitrogen in a 110°C oil bath for 6 hrs. The condenser was replaced with a distillation head and 3.22 g (60%) of colorless 2,2-difluorovaleryl chloride was collected: bp 96°; 'H NMR ($CDCl_3$) δ 1.03 (t, *J* = 7 Hz, 3H), 1.48-1.65 (m, 2H), 2.03-

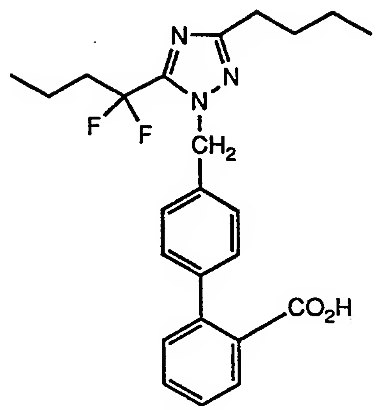
2.23 (m, 2H); ^{19}F NMR ($CDCl_3$) δ -102.41 (t, J = 18 Hz, 2F). The 2,2-difluorovaleryl chloride (20.6 mmol) was dissolved in 10 mL of methylene chloride and dropwise to a solution of 135 g (42 mmol) of anhydrous hydrazine in 20 mL of methylene chloride at 0°C. After the addition was complete, the reaction was stirred at ambient temperature for 1 h, washed with water, dried ($MgSO_4$), and concentrated to give 3.12 g (91%) of 2,2-difluorovaleric acid hydrazide: NMR ($CDCl_3$) δ 0.96 (t, J = 7 Hz, 3H), 1.40-1.56 (m, 2H), 1.96-2.17 (m, 2H), 3.93 (br s, 2H), 7.67 (br s, 1H). A 2.84 g (18.7 mmol) sample of the crude hydrazide was dissolved in 50 mL of methanol and treated with 2.41 g (18.7 mmol) of ethyl iminovalerate. Under nitrogen, the reaction was stirred at reflux for 3 days and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500A) using ethyl acetate/hexane (60:40) gave 3.0 g (74%) of 3-butyl-5-(1,1-difluoro)butyl-1H-1,2,4-triazole as a colorless solid: mp 92-93°C; ^1H NMR ($CDCl_3$) δ 0.97 (t, J = Hz, 3H), 0.92 (t, J = 7 Hz, 3H), 1.30-1.45 (m, 2H), 1.47-1.62 (m, 2H), 1.66-1.81 (m, 2H), 2.18-2.36 (m, 2H), 2.83 (t, J = 7 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ -97.27 (t, J = 18 Hz, 2F); MS (FAB) m/e (rel intensity) 218 (100), 198 (8), 188 (5), 178 (8), 170 (5); HRMS. Calcd for M+H: 218.1469. Found: 218.1461.

Step 2: Preparation of 5-[4'-[[5-butyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid

Under a static nitrogen atmosphere, 2.0 g (9.2 mmol) of solid 3-butyl-5-(1,1-difluorobutyl)-1H-1,2,4-triazole is added in small portions to 10 mmol of sodium hydride in 50 ml of dimethylformamide (DMF); stirring is continued until hydrogen evolution has ceased. The anion solution is cooled to -10°C (ice/methanol) and is treated with a solution of 3.0 g (9.2 mmol) of 4-bromomethyl-2'-methoxycarbonylbiphenyl (from Step 1 of Example 1) in 20 ml of dry DMF. The reaction is allowed to warm to ambient

temperature and stir overnight. Methanol (10 ml) is added to destroy any unreacted sodium hydride and the DMF is removed in vacuo; the residue is dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$). Silica gel chromatography separates the two isomers; the more abundant isomer is dissolved in 80 ml of ethanol and is treated with 80 ml of 10% NaOH at ambient temperature for 3 days. The ethanol is removed in vacuo and the aqueous phase is acidified to pH 1 with hydrochloric acid which causes the product to precipitate; filtration and drying in vacuo gives 4'-[(5-butyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid.

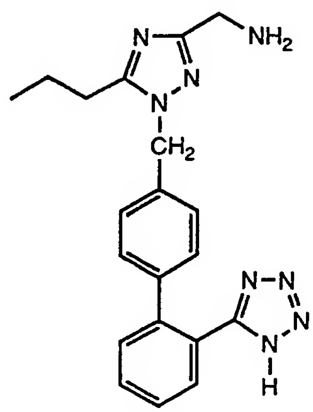
Example 11



4'-[[3-butyl-5-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid

The less abundant isomer isolated in Example 10 is dissolved in 40 ml of ethanol and is treated with 40 ml of 10% NaOH at ambient temperature for 3 days. The ethanol is removed in vacuo and the aqueous phase is acidified to pH 1 with hydrochloric acid which causes the product to precipitate; filtration and drying in vacuo gives 4'-[(3-butyl-5-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid.

Example 12



5-[4'-[(3-aminomethyl-5-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Step 1: Preparation of 5-propyl-3- tert-butoxycarbonylamino-methyl-1H-1,2,4-triazole.

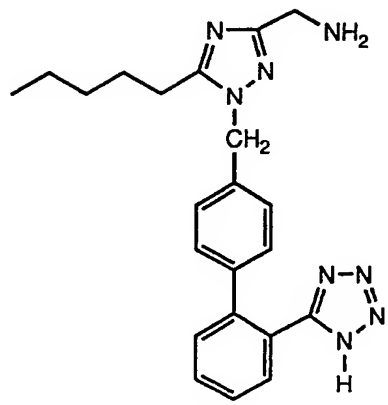
Under nitrogen, a solution of 18.9 g (100 mmol) of N-Boc glycine hydrazide (from step 2 of Example 3) in 100 mL of methanol is treated with 11.5 g (100 mmol) of ethyl iminobutyrate [P. Reynaud and R. C. Moreau, Bull. Soc. Chim. France, 2997 (1964)]. The reaction is stirred at reflux overnight and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500A) gives 5-propyl-3-tert-butoxycarbonylaminomethyl-1H-1,2,4-triazole.

Step 2: Preparation of 5-[4'-[(3-aminomethyl-5-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

Under a static nitrogen atmosphere, 3.81 g (15.0 mmol) of 3-propyl-5-tert-butoxy-carbonylaminomethyl-1H-1,2,4-triazole is added to 15 mmol of sodium hydride in 50 mL of DMF; stirring is continued until hydrogen evolution has ceased. The anion solution is cooled to -10°C

(ice/methanol) and treated with a solution of 8.45 g (15 mmol) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-2-yl)]tetrazole in 20 mL of dry DMF. The reaction is allowed to warm to ambient temperature and stir overnight. Methanol (10 mL) is added to destroy any unreacted sodium hydride and the DMF is removed <u>in vacuo</u>. The residue is dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$). Purification by silica gel chromatography gives the desired isomer which is dissolved in 100 mL of TFA and is stirred at ambient temperature overnight. The reaction is cooled to 0°C, 50 mL of water is added and is allowed to stir at ambient temperature overnight. The solvent is removed <u>in vacuo</u> and the residue is dissolved in acetonitrile/water. Purification by reverse phase chromatography (Waters Delta Prep-3000) provides pure 5-[4'-[(3-aminomethyl-5-propyl-1H-1,2,4-triazole-1-yl][1,1'-biphenyl]-2-yl]-1H-tetrazole as the TFA salt.

Example 13



5-[4'-[(3-aminomethyl-5-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Step 1: Preparation of 5-pentyl-3- tert-butoxycarbonylamino-methyl-1H-1,2,4-triazole.

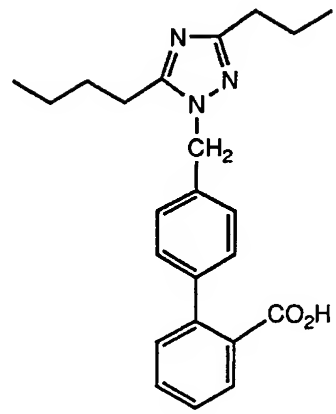
Under nitrogen, a solution of 18.9 g (100 mmol) of N-Boc glycine hydrazide (from step 2 of Example 3) in 100 mL of methanol is treated with 14.3 g (100 mmol) of ethyl iminocaproate [P. Reynaud and R. C. Moreau, Bull. Soc. Chim. France, 2997 (1964)]. The reaction is stirred at reflux overnight and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500A) gives 5-pentyl-3-tert-butoxycarbonylaminomethyl-1H-1,2,4-triazole.

Step 2: Preparation of 5-[4'-[(3-aminomethyl-5-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

Under a static nitrogen atmosphere, 4.02 g (15.0 mmol) of 3-pentyl-5-tert-butoxy-carbonylaminomethyl-1H-1,2,4-triazole is added to 15 mmol of sodium hydride in 50 mL of DMF; stirring is continued until hydrogen evolution has ceased. The anion solution is cooled to -10°C

(ice/methanol) and treated with a solution of 8.45 g (15 mmol) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-2-yl)]tetrazole in 20 mL of dry DMF. The reaction is allowed to warm to ambient temperature and stir overnight. Methanol (10 mL) is added to destroy any unreacted sodium hydride and the DMF is removed in vacuo. The residue is dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$). Purification by silica gel chromatography gives the desired isomer which is dissolved in 100 mL of TFA and is stirred at ambient temperature overnight. The reaction is cooled to 0°C, 50 mL of water is added and is allowed to stir at ambient temperature overnight. The solvent is removed in vacuo and the residue is dissolved in acetonitrile/water. Purification by reverse phase chromatography (Waters Delta Prep-3000) provides pure 5-[4'-[(3-aminomethyl-5-pentyl-1H-1,2,4-triazole-1-yl][1,1'-biphenyl]-2-yl]-1H-tetrazole as the TFA salt.

Example 14



4'-[(5-butyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid

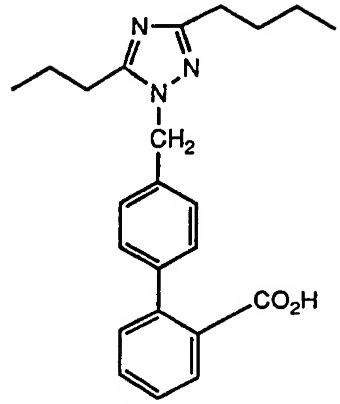
Step 1: Preparation of 5-butyl-3-propyl-1H-1,2,4-triazole.

A 3.95 g (38.7 mmol) sample of butyric acid hydrazide was dissolved in 30 mL of methanol and treated with 5.0 g (38.8 mmol) of ethyl iminovalerate under nitrogen. The reaction was stirred at reflux for 3 days and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500A) using ethyl acetate/hexane (80:20) gave 5.51 g (85%) of 5-butyl-3-propyl-1H-1,2,4-triazole as a colorless solid: mp 48.5-50.0°C; NMR ($CDCl_3$) δ 0.92 (t, *J* = 7 Hz, 3H), 0.97 (t, *J* = 7 Hz, 3H), 1.31-1.46 (m, 2H), 1.66-1.84 (m, 4H), 2.72 (t, *J* = 7 Hz, 2H), 2.75 (t, *J* = 7 Hz, 2H); MS (FAB) m/e (rel intensity) 168 (100), 166 (4), 152 (3), 138 (3), 125 (3); HRMS. Calcd for M+H: 168.1501. Found: 168.1534.

Step 2: Preparation of 4'-[(5-butyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid.

Under a static nitrogen atmosphere, 2.0 g (12 mmol) of solid 5-butyl-3-propyl-1H-1,2,4-triazole is added in small portions to 12 mmol of sodium hydride in 50 ml of dimethylformamide (DMF); stirring is continued until hydrogen evolution has ceased. The anion solution is cooled to -10°C (ice/methanol) and treated with a solution of 3.8 g (12 mmol) of 4-bromomethyl-2'-methoxycarbonylbiphenyl (from Step 1 of Example 1) in 20 ml of dry DMF. The reaction is allowed to warm to ambient temperature and stir overnight. Methanol (10 ml) is added to destroy any unreacted sodium hydride and the DMF is removed in vacuo. The residue is dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$). Silica gel chromatography produces a mixture of the two isomers which is dissolved in 80 ml of ethanol and is treated with 80 ml of 10% nAOH at ambient temperature for 3 days. The thanol is removed in vacuo and the aqueous phase is acidified to pH 1 with hydrochloric acid which causes the mixture of product isomers to precipitate. Purification by reverse phase chromatography (Waters Delta Prep-3000) gives the 5-butyl-3-propyl isomer.

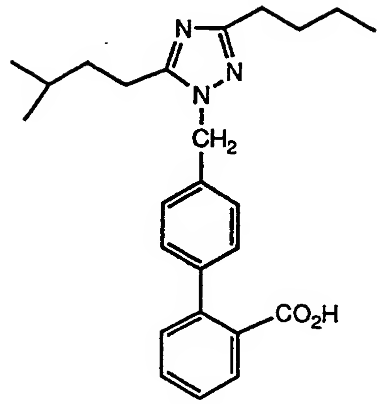
Example 15



4'-[(3-butyl-5-propyl-1H-1,2,4-triazol-1-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid

The other isomer for Example 14 is isolated in an identical manner and provides the 3-butyl-5-propyl isomer.

Example 16



4'-[(3-butyl-5-isopentyl-1H-1,2,4-triazol-1-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid

Step 1: Preparation of 3-butyl-5-isopentyl-1H-1,2,4-triazole.

Under nitrogen, a solution of 53.8 g (1.68 mol) of anhydrous hydrazine in 300 mL of methanol was cooled to 0°C and treated with 186 g (1.4 mol) of methyl 4-methylvalerate. The reaction was allowed to warm to ambient temperature and stir overnight prior to stirring at reflux for 4 h. The reaction was concentrated *in vacuo* giving 166 g (93%) of 4-methylvaleric acid hydrazide as a colorless solid: 49-51°C; NMR ($CDCl_3$) δ 0.89 (d, *J* = 7 Hz, 6H), 1.48-1.64 (m, 3H), 2.15 (t, *J* = 7 Hz, 2H), 3.91 (br s, 2H), 6.94 (br s, 1H). A 7.86 g (60 mmol) sample of the

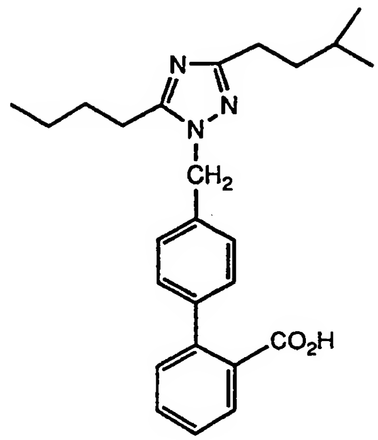
hydrazide was dissolved in 50 mL of methanol and treated with 7.8 g (60 mmol) of ethyl iminovalerate under nitrogen. The reaction was stirred at reflux overnight and concentrated _in vacuo_. Purification by silica gel chromatography (Waters Prep-500A) using ethyl acetate/hexane (40:60) gave 9.6 g (82%) of 3-butyl-5-isopentyl-1H-1,2,4-triazole as a colorless solid which melts close to ambient temperature: NMR ($CDCl_3$) δ 0.81-0.90 (m, 9H), 1.25-1.40 (m, 2H), 1.47-1.74 (m, 5H), 2.70 (t, _J_ = 7 Hz, 4H); MS (FAB) m/e (rel intensity) 196 (100); HRMS. Calcd for M+H: 196.1814. Found: 196.1832.

Step 2: Preparation of 4'-[(3-butyl-5-isopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid.

Under a static nitrogen atmosphere, 2.0 g (10.3 mmol) of solid 3-butyl-5-isopentyl-1H-1,2,4-triazole is added in small portions to 11 mmol of sodium hydride in 50 ml of dimethylformamide (DMF); stirring is continued until hydrogen evolution has ceased. The anion solution is cooled to -10°C (ice/methanol) and is treated with a solution of 3.27 g (10.2 mmol) of 4-bromomethyl-2'-methoxycarbonylbiphenyl (from Step 1 of Example 1) in 20 ml of dry DMF. The reaction is allowed to warm to ambient

temperature and stir overnight. Methanol (10 ml) is added to destroy any unreacted sodium hydride and the DMF is removed _in vacuo_. The residue is dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$). The crude material is dissolved in 80 ml of ethanol and is treated with 80 ml of 10% NaOH at ambient temperature for 3 days. The ethanol is removed _in vacuo_ and the aqueous phase is acidified to pH 1 with hydrochloric acid which causes the mixture of product isomers to precipitate purification by reverse phase chromatography (Waters Delta Prep-3000) give sthe 3-butyl-5-isopentyl isomer.

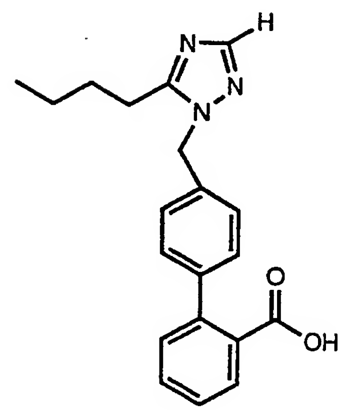
Example 17



4'-[(5-butyl-3-isopentyl-1H-1,2,4-triazol-1-yl]methyl)-[1,1'-biphenyl]-2-carboxylic acid

The other isomer from Example 16 is isolated in an identical manner and provides the 5-butyl-3-isopentyl isomer.

Example 18

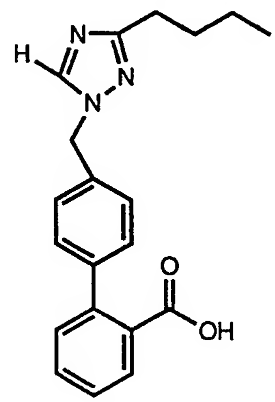


4'-[(5-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid

Following General Procedure A, 5.0 g (39.9 mmol) of 5-butyl-1H-1,2,4-triazole was coupled with 12.2 g (39.9 mmol) of the alkylating reagent prepared in step 1 of Example 1 to give 3.1 g (22%) of a faster moving isomer: NMR ($CDCl_3$) δ 0.90 (t, *J* = 8 Hz, 3H), 1.29-1.45 (m, 2H), 1.63-1.76 (m, 2H), 2.71 (t, *J* = 8 Hz, 2H), 3.62 (s, 3H), 5.34 (s, 2H), 7.14-7.20 (m, 2H), 7.24-7.33 (m, 3H), 7.40 (dt, *J* = 8 and 2 Hz, 1H), 7.50 (dt, *J* = 8 and 2 Hz, 1H), 7.82 (dd, *J* = 8 and 2 Hz, 1H), 7.85 (s, 1H) and 3.7 g (26%) of a slower moving isomer: NMR ($CDCl_3$) δ 0.92 (t, *J* = 8 Hz, 3H), 1.31-1.46 (m, 2H), 1.66-1.79 (m, 2H), 2.73 (t, *J* = 8 Hz, 2H), 3.62 (s, 3H), 5.28 (s, 2H), 7.21-7.34 (m, 5H), 7.39 (dt, *J* = 8 and 2 Hz, 1H), 7.50 (dt, *J* = 8 and 2 Hz, 1H), 7.83 (dd, *J* = 8 and 2 Hz, 1H), 7.94 (s, 1H). The faster moving isomer was hydrolyzed to give 2.75 g (92%) of 4'-[(5-butyl-1H-1,2,4-triazol-1-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid as a colorless solid: NMR (DMSO-d_6) δ 0.85 (t, *J* = 8 Hz, 3H), 1.23-1.38 (m, 2H), 1.52-1.65 (m, 2H), 2.76 (t, *J* = 7 Hz, 2H), 5.41 (s, 2H), 7.16-7.24 (m, 2H), 7.27-7.37 (m, 3H), 7.44 (dt, *J* = 8 and 2 Hz, 1H), 7.56

(dt, $\underline{J}$ = 8 and 2 Hz, 1H), 7.72 (dd, $\underline{J}$ = 8 and 2 Hz, 1H), 7.86 (s, 1H); MS (FAB) m/e (rel intensity) 336 (100), 307 (7), 289 (7), 224 (8), 211 (100), 193 (9).

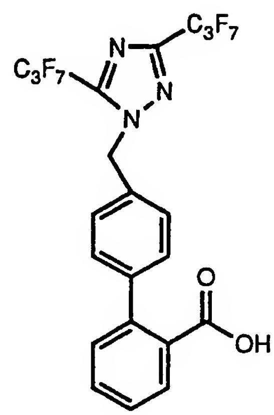
Example 19



4'-[(3-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid

The slower moving isomer from Example 18 was hydrolyzed to give 2.3 g (67%) of 4'-[(3-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid as a colorless solid: NMR (DMSO-d_6) δ 0.87 (t, J = 8 Hz, 3H), 1.23-1.38 (m, 2H), 1.54-1.67 (m, 2H), 2.58 (t, J = 8 Hz, 2H), 5.36 (s, 2H), 7.23-7.38 (m, 5H), 7.44 (dt, J = 8 and 2 Hz, 1H), 7.56 (dt, J = 8 and 2 Hz, 1H), 7.72 (dd, J = 8 and 2 Hz, 1H), 8.51 (s, 1H); MS (FAB) m/e (rel intensity) 336 (85), 211 (100), 165 (24), 126 (52).

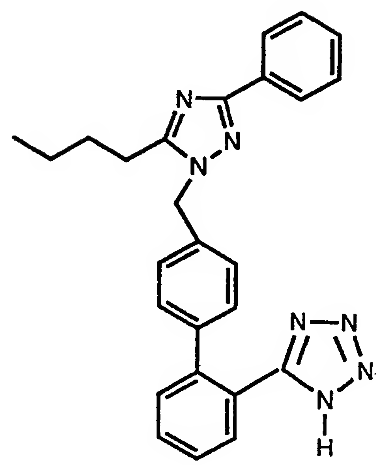
Example 20



4'-[(3,5-di-perfluoropropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid

Following General Procedure A, 11.0 g (27.2 mmol) of 3,5-bis(perfluoropropyl)-1H-1,2,4-triazole was coupled with 8.30 g (27.2 mmol) of the alkylating reagent prepared in step 1 of Example 1 to give 8.7 g (51%) of a colorless oil: NMR ($CDCl_3$) δ 3.62 (s, 3H), 5.63 (s, 2H), 7.25-7.37 (m, 5H), 7.44 (dt, *J* = 8 and 2 Hz, 1H), 7.54 (dt, *J* = 8 and 2 Hz, 1H), 7.87 (dd, *J* = 8 and 2 Hz, 1H). A 8.5 g (13.5 mmol) sample of this material was hydrolyzed to give 6.91 g (81%) of 4'-[(3,5-bis(1,1,2,2,3,3,3-heptafluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxlic acid as a colorless solid: NMR ($CDCl_3$) δ 5.62 (s, 2H), 7.27-7.37 (m, 5H), 7.44 (dt, *J* = 8 and 2 Hz, 1H), 7.58 (dt, *J* = 8 and 2 Hz, 1H), 7.98 (dd, *J* = 8 and 2 Hz, 1H); MS (TSP) M+NH_4 (rel intensity) 633 (100), 211 (12); HRMS. Calc'd for M+Li: 622.0788. Found: 622.0759.

Example 21

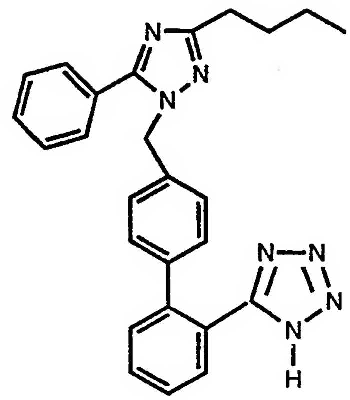


5-[4'-[(3-phenyl-5-butyl-1H-1,2,4-triazol-1-yl)methyl](1,1'-biphenyl)-2-yl]-1H-tetrazole

Following General Procedure A, 2.0 g (9.9 mmol) of 5-butyl-3-phenyl-1H-1,2,4 triazole was coupled with 5.5 g (9.9 mmol) of the alkylating reagent prepared in step 1 of Example 3 to give 5.2 g (77%) of a faster moving isomer: NMR ($CDCl_3$) δ 0.90 (t, *J* = 8 Hz), 1.30-1.44 (m, 2H), 1.63-1.77 (m, 2H), 2.67 (t, *J* = 8 Hz, 2H), 5.24 (s, 2H), 6.88-7.01 (m, 8H), 7.08-7.53 (m, 17H), 7.95 (dd, *J* = 8 and 2 Hz, 1H), 8.12 (dd, *J* = 8 and 2 Hz, 2H) and 420 mg (6.3%) of a slower moving isomer: NMR ($CDCl_3$) δ 0.96 (t, *J* = 8 Hz, 3H), 1.38-1.52 (m, 2H), 1.75-1.89 (m, 2H), 2.84 (t, *J* = 8 Hz, 2H), 5.27 (s, 2H), 6.88-6.97 (m, 8H), 7.13 (d, *J* = 8 Hz, 2H), 7.17-7.54 (m, 15H), 7.57 (d, *J* = 8 Hz, 2H), 7.93 (dd, *J* = 8 and 2 Hz, 1H). A 4.8 g (7.1 mmol) sample of the faster moving isomer was deportected to give 1.64 g (53%) of 5-[4'-[(3-phenyl-5-butyl-1H-1,2,4-triazol-1-yl)methyl](1,1'-biphenyl-2-yl]-1H-tetrazole as a colorless solid: mp 113 °C (dec); NMR ($CDCl_3$) δ 0.87 (t, *J* = 8 Hz, 3H), 1.24-1.39 (m, 2H),1.55-1.69 (m, 2H), 2.60 (t, *J* = 8 2Hz, 5.19 (s, 2H), 7.04 (d, *J* = 8 Hz, 2H), 7.11 (d, *J* = 8

Hz, 2H), 7.27-7.39 (m, 4H), 7.47-7.60 (m, 2H), 7.87 (dd, *J* = 8 and 2 Hz, 2H), 7.95 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 436 (100), 393 (8), 207 (60), 192 (20), 178 (13), 165 (8); HRMS. Calc'd for M+H: 436.2249. Found: 436.2240.

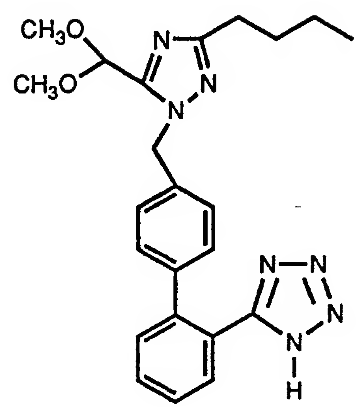
Example 22



5-[4'-[(3-butyl-5-phenyl-1H-1,2,4-triazol-1-yl)methyl](1,1'-biphenyl)-2-yl]-1H-tetrazole

The slower moving isomer from Example 21 was deprotected to give 251 mg (60%) of 5-[4'-[(3-butyl-5-phenyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: mp 205 °C (dec); NMR ($CDCl_3$) δ 0.88 (t, *J* = 8 Hz, 3H), 1.23-1.38 (m, 2H), 1.55-1.68 (m, 2H), 2.52 (t, *J* = 8 Hz, 2H), 5.32 (s, 2H), 6.99 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H), 7.31-7.61 (m, 8H), 7.90 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 436 (100), 393 (9), 374 (7), 277 (7), 247 (15), 207 (45); HRMS. Calc'd for M+H: 436.2249. Found: 436.2201.

Example 23

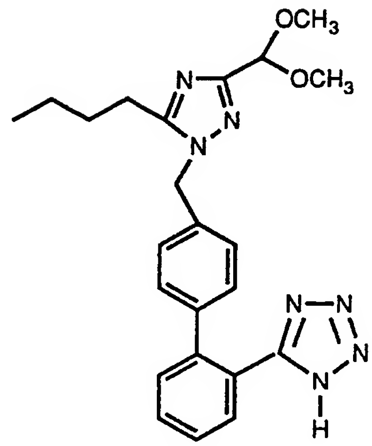


5-[4'-[[3-butyl-5-(dimethoxymethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following General Procedure A, 2.0 g (10 mmol) of 5-butyl-3-(dimethoxymethyl)-1H-1,2,4-triazole was coupled with 5.6 g (10 mmol) of the alkylating regagent prepared in step 1 of Example 3 to give 1.65 g (24%) of a faster moving isomer: NMR ($CDCl_3$) δ 0.92 (t, *J* = 8 Hz, 3H), 1.31-1.45 (m, 2H), 1.66-1.78 (m, 2H), 2.69 (t, *J* = 8 Hz, 2H), 3.33 (s, 6H), 5.30 (s, 2H), 5.42 (s, 1H), 6.90-6.96 (m, 5H), 7.02-7.12 (m, 4H), 7.21-7.38 (m, 11H), 7.41-7.52 (m, 2H), 7.86-7.92 (m, 1H) and 3.65 g (54.0%) of a slower moving isomer: NMR ($CDCl_3$) δ 0.85 (t, *J* = 8 Hz, 3H), 1.22-1.36 (m, 2H), 1.57-1.70 (m, 2H), 2.59 (t, *J* = 8 Hz, 2H), 3.45 (s, 6H), 5.20 (s, 2H), 5.55 (s, 1H), 6.89-6.97 (m, 5H), 7.08-7.19 (m, 4H), 7.21-7.37 (m, 11H), 7.41-7.52 (m, 2H), 7.90-7.95 (m, 1H). The faster moving isomer was deprotected to give 737 mg (70%) of 5-[4'-[[3-butyl-5-(dimethoxymethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: mp 152.5-153.5 °C; NMR ($CDCl_3$) δ 0.87 (t, *J* = 8 Hz, 3H), 1.20-1.30 (m, 2H), 1.53-1.65 (m, 2H), 2.46 (t, *J* = 8 Hz, 2H), 3.30 (s, 6H), 5.37 (s, 2H), 5.40 (s, 1H), 7.05-8.05 (m,

4H), 7.45 (dd, *J* = 8 and 2 Hz, 1H), 7.51-7.65 (m, 2H), 8.02 (d, *J* = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 434 (65), 402 (40), 370 (11), 342 (46), 249 (85), 235 (18), 207 (100), 192 (89), 168 (70); HRMS. Calc'd for M+H: 434.2304. Found: 434.2332.

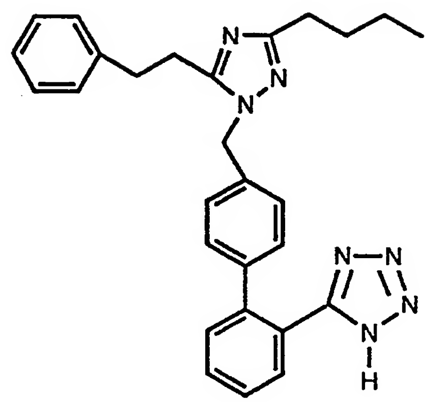
Example 24



5-[4'-[(5-butyl-3-dimethoxymethyl-1H-1,2,4-triazol-1-yl)methyl](1,1'-biphenyl-2-yl]-1H-tetrazole

A 3.65 g (5.4 mmol) sample of the slower moving isomer from Example 23 was deprotected to give 108 mg of colorless 5-[4'-[[5-butyl-3-(dimethoxymethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole after lyophilization: NMR ($CDCl_3$) δ 0.86 (t, *J* = 8 Hz, 3H), 1.24-1.39 (m, 2H), 1.56-1.70 (m, 2H), 2.66 (t, *J* = 8 Hz, 2H), 3.30 (s, 6H), 5.23 (s, 2H), 5.35 (s, 1H), 7.02 (d, *J* = 8 Hz, 2H), 7.10 (d, *J* = 8 Hz, 2H), 7.40 (dd, *J* = 8 and 2 Hz, 1H), 7.51 (dt, *J* = 8 and 2 Hz, 1H), 7.59 (dt, *J* = 8 and 2 Hz, 1H), 7.89 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 434 (10), 402 (40), 249 (100), 207 (36), 192 (54), 168 (12); HRMS. Calc'd for M+H: 434.2304. Found: 434.2271.

Example 25

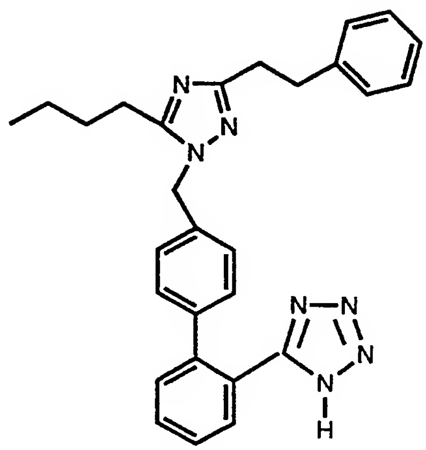


5-[4'-[(3-butyl-5-phenylethyl-1H-1,2,4-triazol-1-yl)methyl](1,1'-biphenyl-2-yl]-1H-tetrazole

Following General Procedure A, 2.3 g (10 mmol) of 3-butyl-5-phenethyl-1H-1,2,4-triazole was coupled with 6.6 g (10 mmol) of the alkylating reagent prepared in step 1 of Example 3 to give 2.67 g (38%) of a faster moving isomer: NMR ($CDCl_3$) δ 0.97 (t, *J* = 8 Hz, 3H), 1.36-1.50 (m, 2H), 1.71-1.84 (m, 2H), 2.73 (t, *J* = 8 Hz, 2H), 2.78-2.88 (m, 2H), 2.92-3.01 (m, 2H), 4.82 (s, 2H), 6.80-6.95 (m, 9H), 7.02-7.11 (m, 5H), 7.16-7.36 (m, 11H), 7.41-7.52 (m, 2H), 7.91-7.97 (m, 1H) and 2.94 g (42%) of a slower moving isomer: NMR ($CDCl_3$) δ 0.88 (t, *J* = 8 Hz, 3H), 1.23-1.38 (m, 2H), 1.57-1.70 (m, 2H), 2.58 (t, *J* = 8 Hz, 2H), 2.97-3.13 (m, 4H), 5.11 (s, 2H), 6.86 (d, *J* = 8 Hz, 2H), 6.89-6.96 (m, 6H), 7.10 (d, *J* = 8 Hz, 2H), 7.14-7.39 (m, 15H), 7.42-7.54 (m, 2H), 7.93 (dd, *J* = 8 and 2 Hz, 1H). The faster moving isomer was deprotected to give 1.6 g (88%) of 5-[4'-[[3-butyl-5-(2-phenylethyl)-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl-2-yl]-1H-tetrazole a colorless solid: NMR ($CDCl_3$) δ 0.86 (t, *J* = 8 Hz, 3H), 1.17-1.31 (m, 2H), 1.48-1.51 (m, 2H), 2.42 (t, *J* = 8 Hz, 2H), 2.76 (t, *J* = 8 Hz, 2H), 2.92 (t, *J* = 8 Hz, 2H), 4.80 (s, 2H), 6.83 (d,

J = 8, 2H), 6.92-7.00 (m, 2H), 7.08 (d, *J* = 8 Hz, 2H), 7.17-7.32 (m, 3H), 7.42 (dd, *J* = 8 and 2 Hz, 1H), 7.51-7.65 (m, 2H), 7.96 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 464 (37), 230 (25), 207 (100), 178 (17); HRMS. Calc'd for M+H: 464.2563. Found: 464.2532.

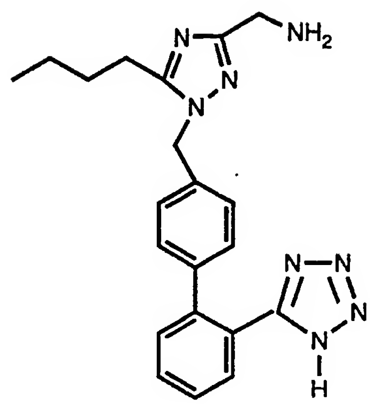
Example 26



5-[4'[(5-butyl-3-phenylethyl-1H-1,2,4-triazol-1-yl)methyl](1,1'-biphenyl-2-yl]-1H-tetrazole

The slower moving isomer from Example 25 was deprotected to give 1.5 g (77%) of 5-[4'-[[5-butyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl-2-yl]-1H-tetrazole as a colorless solid: mp 156.0-157.2°C; NMR ($CDCl_3$) δ 0.84 (t, J = 8 Hz, 3H), 1.19-1.34 (m, 2H), 1.47-1.61 (m, 2H), 2.52 (t, J = 8 Hz, 2H), 2.66-2.77 (m, 2H), 2.85-2.95(m, 2H), 5.15 (s, 2H), 6.88 (d, J = 8 Hz, 2H), 7.05-7.11(m, 4H), 7.12-7.28(m, 5H), 7.41 (dd, J = 8 and 2 Hz, 1H), 7.50 (dt, J = 8 and 2 Hz, 1H), 7.59 (dt, J = 8 and 2 Hz, 1H), 7.92 (dd, J = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 464 (83), 230 (22), 207 (92); HRMS. Calc'd for M+H: 464.2563. Found: 464.2560.

Example 27

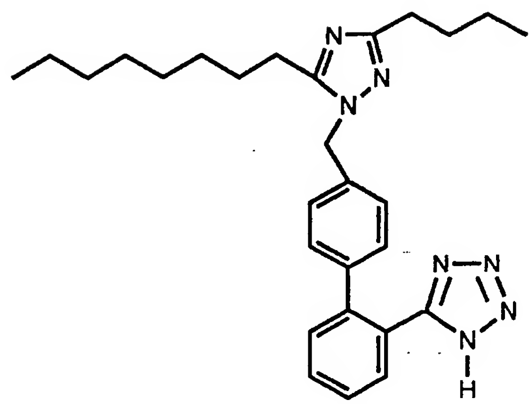


5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-3-methanamine

A 1.5 g (3.5 mmol) sample of the diacetal compound of Example 24 was dissolved in 40 ml of ethanol and 40 ml of 3N HCl. The reaction was stirred at ambient temperature overnight and then at reflux for 50 min, the course of the reaction was followed by analytical reverse phase HPLC. The solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and extracted with saturated sodium bicarbonate solution until the water layer stayed basic. The water layer was acidified and extracted with an ethyl acetate/methylene chloride mixture. The organic layer was dried ($MgSO_4$) and removed *in vacuo* yielding 0.96 g of crude aldehyde: NMR ($CDCl_3$) δ 0.66 (t, J = 8 Hz, 3H), 1.06-1.20 (m, 2H), 1.42-1.54 (m, 2H), 2.53 (t, J = 8 Hz, 2H), 5.17 (s, 2H), 6.80-6.95 (m, 4H), 7.17-7.38 (m, 3H), 7.42-7.48 (m, 1H), 9.70 (s, 1H). Under a static nitrogen atmosphere, 0.91 g (2.3 mmol) of this material was dissolved in 10 ml of methanol and 1.77 g (23 mmol) ammonium acetate was added followed by 0.10 g (1.61 mmol) sodium cyanoborate. After stirring at ambient temperature for 3 days, analytical reverse phase HPLC indicated that the reaction was complete. Purification was accomplished

by reverse phase chromatography (Waters Delta Prep 3000) using 25% acetonitrile/water (0.05% TFA). The solvent from the pure fractions was removed in vacuo and the residue dissolved in methanol and 3N HCl. After stirring for 30 min, the solvent was removed in vacuo and the residue lyophilized from acetonitrile/water providing 100 mg (10%) of 5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-3-methanamine as the colorless hydrochloride salt: NMR (DMSO-d_6) δ 0.85 (t, *J* = 8 Hz, 3H), 1.22-1.38 (m, 2H), 1.51-1.64 (m, 2H), 2.77 (t, *J* = 8 Hz, 2H), 4.00-4.09 (m, 2H), 5.40 (s, 2H), 7.01-7.25 (m, 4H), 7.39 (s, 1H), 7.48-7.73 (m, 3H); MS (FAB) m/e (rel intensity) 389 (100), 207 (65), 192 (17); HRMS. Calc'd for M+H: 389.2202. Found: 389.2170.

Example 28

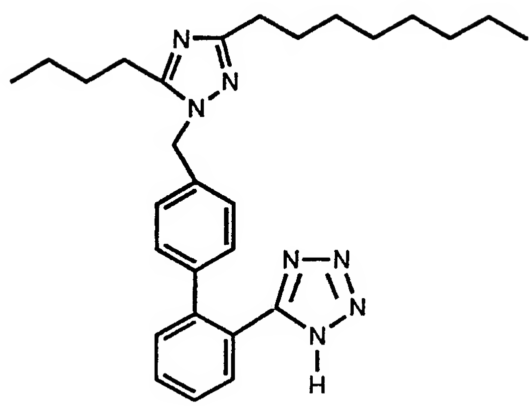


5-[4'-[(3-butyl-5-octyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following General Procedure A, 2.0 g (8.4 mmol) of 3-butyl-5-octyl-1H-1,2,4-triazole was coupled with 5.5 g (8.4 mmol) of the alkylating reagent prepared in step 1 of Example 3. Silica gel chromatography (Waters Prep 500-A) using 25% ethyl acetate/hexane produced 4.5 g (75.4%) of a mixture of the two isomers which was dissolved in 40 ml of 10% water/acetic acid and stirred at ambient temperature overnight. The solvent was removed in vacuo. Purification of a sample of the isomeric product mix by reverse phase chromatography (Waters Delta Prep-3000) using 45% acetonitrile/water (0.05% TFA) for 30 minutes followed by 50% acetonitrile/water (0.05% TFA) provided two isomers. The faster moving isomer compound was dissolved in dilute base, the water was acidified (pH 4-5) with 1N HCl, and the product extracted with ethyl acetate. The ethyl acetate was dried ($MgSO_4$) and removed in vacuo yielding a solid which was recrystallized from acetonitrile providing 92 mg of 5-[4'-[(3-butyl-5-octyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: mp 136.5-138.0°C; NMR ($CDCl_3$) δ 0.82 (t,

J = 8 Hz, 3H), 0.86 (t, J = 8 Hz, 3H), 1.11-1.33 (m, 12H), 1.40-1.60 (m, 4H), 2.27 (t, J = 8 Hz, 2H), 2.44 (t, J = 8 Hz, 2H), 5.16 (s, 2H), 6.87 (d, J = 8 Hz, 2H), 7.07 (d, J = 8 Hz, 2H), 7.44 (dd, J = 8 and 2 Hz, 1H), 7.50-7.66 (m, 2H), 7.90 (dd, J = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 472 (5), 207 (7); HRMS. Calc'd for M+H: 472.3189. Found: 472.3180.

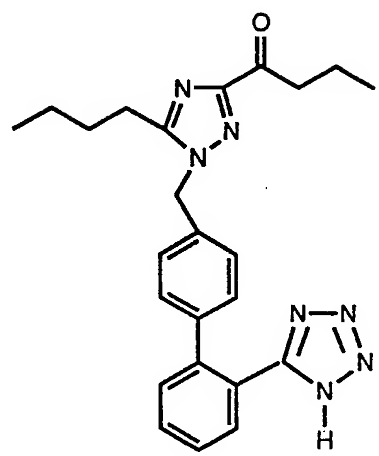
Example 29



5-[4'-[(5-butyl-3-octyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

The slower moving isomer from Example 28 was isolated in an identical manner and the product lyophilized from acetonitrile/water providing 53 mg of 5-[4'-[(5-butyl-3-octyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: NMR ($CDCl_3$) δ 0.83 (t, *J* = 8 Hz, 3H), 0.86 (t, *J* = 8 Hz, 3H), 1.12-1.37 (m, 12H), 1.46-1.63 (m, 4H), 2.35 (t, *J* = 8 Hz, 2H), 2.51 (t, *J* = 8 Hz, 2H), 5.19 (s, 2H), 6.92 (d, *J* = 8 Hz, 2H), 7.09 (d, *J* = 8 Hz, 2H), 7.40-7.48 (m, 1H), 7.51-7.66 (m, 2H), 7.91 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 472 (6), 207 (8); HRMS. Calc'd for M+H: 472.3189. Found: 472.3230.

Example 30



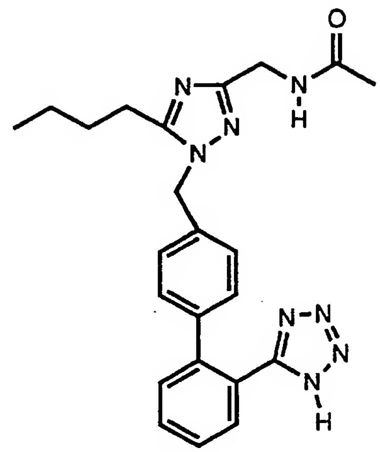
1-[[5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-3-yl]methyl]-1-butanone

Under a static nitrogen atmosphere, 30.0 g (150 mmol) 5-butyl-3-dimethoxy-1H-1,2,4-triazole (from Step 1 of Example 23 was added in small portions to 165 mmol of sodium hydride in 300 ml anhydrous THF; stirring was continued for 1 h. The anion solution was cooled to -10 °C (methanol/ice) and treated with Sem-Cl dropwise. The reaction was allowed to warm to ambient temperature and stir overnight. The solvent was removed in vacuo. The residue was dissolved in methylene chloride, washed with water, dried ($MgSO_4$), and the solvent removed again in vacuo. Silica gel chromatography using 20% ethyl acetate/hexane followed by ethyl acetate provided 13.6 g of the faster moving isomer as an oil: NMR ($CDCl_3$) δ -0.07 (s, 9H), 0.82-0.92 (m, 5H), 1.26-1.40 (m, 2H), 1.62-1.74 (m, 2H), 2.67 (t, J = 8 Hz, 2H), 3.38 (s, 6H), 3.53-3.62 (m, 2H), 5.47 (s, 2H), 5.55 (s, 1H). Under a static nitrogen atmosphere, 12.6 g (38.2 mmol) of the faster moving Sem-protected triazole isomer from above was dissolved in 630 ml of anhydrous THF, cooled to -78 °C, and

45.8 mmol of sec-butyl lithium was added dropwise. The solution was stirred for 1 h and then the anion was quenched with 4.5 ml (45.8 mmol) of n-propyl iodide. The solution was stirred at -78 °C for 5 h and then allowed to warm to ambient temperature overnight. The solvent was removed in vacuo. The residue was dissolved in methylene chloride, washed with water, dried ($MgSO_4$) and the solvent removed providing 12.4 g of crude Sem-protected 5-butyl-3-(1,1-dimethoxybutane)-1H-1,2,4-triazole: NMR ($CDCl_3$) δ -0.04 (s, 9H), 0.75-0.93 (m, 8H), 0.98-1.11 (m, 2H), 1.25-1.41 (m, 2H), 1.62-1.74 (m, 2H), 1.99-2.08 (m, 2H), 2.68 (t, *J* = 8 Hz, 2H), 3.20 (s, 6H), 3.62 (t, *J* = 8 Hz, 2H), 5.56 (s, 2H). A 1.0 g (2.7 mmol) sample of the crude dimethoxybutyl compound was dissolved in 5 ml of ethanol and 5 ml of 3M HCl and stirred at reflux for 2.5 h. The solvent was removed in vacuo providing 560 mg of the crude HCl salt of 5-butyl-3-(1-butanone)-1H-1,2,4-triazole: NMR (DMSO-d_6) δ 0.83-0.94 (m, 6H), 1.21-1.36 (m, 2H), 1.55-1.75 (m, 4H), 2.83 (t, *J* = 8 Hz, 2H), 2.97 (t, *J* = 8 Hz, 2H). The crude HCl salt of the triazole was dissolved in 20 ml of fresh methanol, 3Å molecular sieves were added, and the mixture stirred at reflux under nitrogen overnight. The solution was filtered through celite and the solvent removed in vacuo. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution. The solvent was dried ($MgSO_4$) and removed in vacuo providing 390 mg of crude 5-butyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazole: NMR ($CDCl_3$) δ 0.90 (t, *J* = 8 Hz, 3H), 0.99 (t, *J* = 8 Hz, 3H), 1.29-1.46 (m, 2H), 1.66-1.84 (m, 4H), 2.80 (t, *J* = 8 Hz, 2H), 3.06 (t, *J* = 8 Hz, 2H), 3.18 (s, 6H). Under a static nitrogen atmosphere, 380 mg (1.6 mmol) of this material in 5 ml of anhydrous dimethylformamide (DMF) was added to 1.9 mmol sodium hydride in 5 ml of DMF; stirring was continued for 1 h. The anion solution was cooled to 0 °C and 890 mg (1.6 mmol) of the alkylating reagent prepared in from step 1 of Example 3 was added as a solid. The reaction was allowed

to warm to ambient temperature and stir overnight. Methanol (1 ml) was added to destroy any unreacted sodium hydride and the DMF was removed _in vacuo_. The residue was dissolved in ethyl acetate, washed with water, and dried ($MgSO_4$). The solvent was removed _in vacuo_ providing 1.2 g of crude material which was dissolved in 10 ml ethanol and 10 ml 3N HCl and stirred at reflux for 2 h. The solvent was removed _in vacuo_. Purification by reverse phase chromatography (Water Delta Prep 3000) using isocratic 37% acetonitrile/water (0.05% TFA) for 40 minutes followed by 50% acetonitrile/water (0.05% TFA) provided the TFA salt. The salt was dissolved in basic water (pH 9-10), the water was acidified to pH 4 with 3N HCl, and the product extracted with ethyl acetate. The ethyl acetate was dried ($MgSO_4$) and removed _in vacuo_ yielding a solid which was recrystallized from acetonitrile providing 146 mg (21%) of 1-[[5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-3-yl]methyl]-1-butanone mp 150.5-152.5°C; NMR ($CDCl_3$) δ 0.85 (t, _J_ = 8 Hz, 3H), 0.96 (t, _J_ = 8 Hz, 3H), 1.23-1.39 (m, 2H), 1.54-1.77 (m, 4H), 2.67 (t, _J_ = 8 Hz, 2H), 2.97 (t, _J_ = 8 Hz, 2H), 5.28 (s, 2H), 7.02 (d, _J_ = 8 Hz, 2H), 7.10 (d, _J_ = 8 Hz, 2H), 7.37 (d, _J_ = 8 Hz, 1H), 7.43-7.62 (m, 2H), 7.86 (d, _J_ = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 430 (6), 207 (12); HRMS. Calc'd for M+H: 430.2355. Found: 430.2404.

Example 31

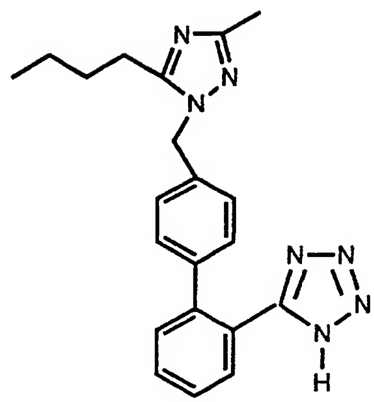


N-[[5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-3-yl]methyl]acetamide

A 92.9 mg (0.22 mmol) sample of 5-[4'-[(5-butyl-3-methylamine-1H-1,2,4-triazol-1-yl)methyl]-(1,1'-biphenyl-2-yl]-1H-tetrazole hydrochloride from Example 27 was dissolved in 5 ml of water and the pH was adjusted to 9 with 1M potassium carbonate (K_2CO_3) . The solution was cooled to 0 °C and 0.22 ml of 1M K_2CO_3 was added followed by 0.22 mmol of acetic anhydride. Additional K_2CO_3 was added as needed to maintain a pH of 9. At 30 min intervals, this addition was repeated until analytical reverse phase chromatography showed that all starting material has been consumed. The pH was adjusted to three with 1N HCl and extracted with ethyl acetate. The ethyl acetate was removed in vacuo and the product lyophilized from acetonitrile/water providing 36 mg (39%) of N-[[5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-3-yl]methyl]acetamide as a colorless solid: NMR ($CDCl_3$) δ 0.80 (t, J = 8 Hz, 3H), 1.18-1.37 (m, 2H), 1.47-1.64 (m, 2H), 1.94 (s, 3H), 2.63 (t, J = 8 Hz, 2H), 4.22 (d, J = 8 Hz, 2H), 5.18 (s, 2H), 6.95 (d, J = 8

Hz, 2H), 7.04-7.21 (m, 2H), 7.44 (d, _J_ = 8 Hz, 1H), 7.50-7.66 (m, 2H), 7.90 (dd, _J_ = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 431 (42), 207 (100); HRMS. Calc'd for M+H: 431.2308. Found: 431.2271.

Example 32

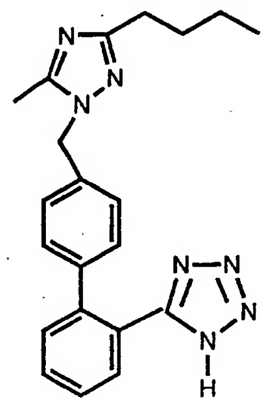


5-[4'-[(5-butyl-3-methyl-1H-1,2,4-triazol-1-yl)methyl]-[1,1'-biphenyl]-2-yl]-1H-tetrazole

Following General Procedure A, 700 mg (5.0 mmol) of 5-butyl-3-methyl-1H-1,2,4-triazole was coupled with 2.8 g (5.0 mmol) of the aklylating reagent prepared in step 1 of Example 3. Silica gel chromatography using ethyl acetate/toluene (35:65) produced 2.75 g (90%) of a mixture of the two isomers which was dissolved in 30 ml 10% water/acetic acid and sitrred at ambient temperature for 3 days. The solvent was removed in vacuo and the residue dissolved in dilute base, washed with toleune, acidified to pH 4 with 1N HCl and the product extracted with ethyl acetate. Purification of the isomeric product mixture by reverse phase chromatography (Water Delta Prep-3000) using isocratic acetonitrile/water (23:77) (0.05% TFA) provided two isomers. The faster moving isomer compound was dissolved in dilute base, acidified to pH 3-4 and extracted with ethyl acetate. The solvent was removed in vacuo; recrystallization from acetonitrile gave 199 mg (12%) of 5-[4'-[(5-butyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl]-[1,1'-

biphenyl]-2-yl]-1H-tetrazole as a colorless solid: mp 170.0-170.5°C; NMR ($CDCl_3$) δ 0.79 (t, *J* = 8 Hz, 3H), 1.18-1.32 (m, 2H), 1.44-1.56 (m, 2H), 1.99 (s, 3H), 2.49 (t, *J* = 8 Hz, 2H), 5.15 (s, 2H), 6.87 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H),7.44 (dd, *J* = 8 and 2 Hz, 1H), 7.51-7.65 (m, 2H), 7.90 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 374 (100), 235 (13), 207 (100), 140 (29); HRMS. Calc'd for M+H: 374.2093. Found: 374.2062.

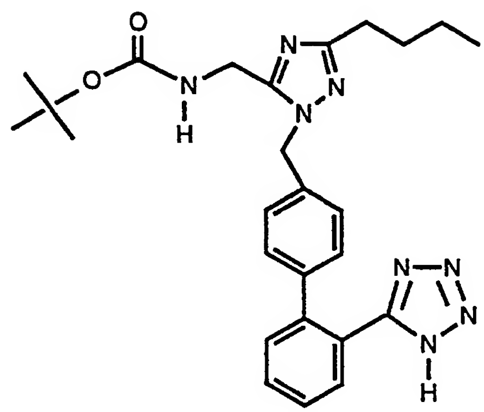
Example 33



5-[4'-[(3-butyl-5-methyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

The slower moving isomer from Example 32 was dissolved in dilute base, acidified to pH 3-4, and extraced with ethyl acetate. The solvent was removed in vacuo and the product lyophilized from acetonitrile/water which gave 536 mg (33 %) of 5-[4'-[(3-butyl-5-methyl-1H-1,2,4-triazol-1-yl)methyl]-[1,1'-biphenyl]-1-yl]-1H-tetrazole as a colorless solid: NMR ($CDCl_3$) δ 0.82 (t, J = 8 Hz, 3H), 1.21-1.35 (m, 2H), 1.53-1.66 (m, 2H), 2.35 (s, 3H), 2.56 (t, J = 8 Hz, 2H), 5.23 (s, 2H), 7.03 (d, J = 8 Hz, 2H), 7.11 (d, J = 8 Hz, 2H), 7.42 (dd, J = 8 and 2 Hz, 1H), 7.47-7.63 (m, 2H), 7.88 (dd, J = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 374 (65), 331 (12), 235 (13), 207 (100), 192 (38), 140 (56); HRMS. Calc'd for M+H: 374.2093. Found: 374.2071.

Example 34

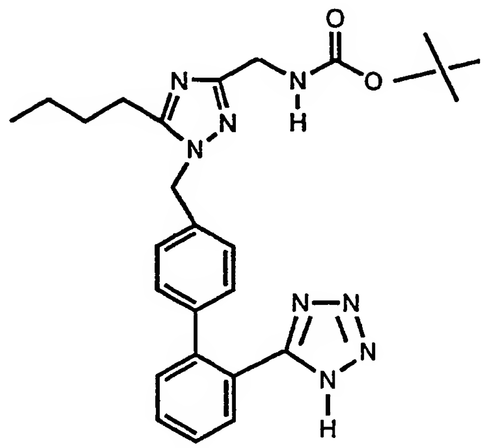


1,1-dimethylethyl [3-butyl-[1-2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-5-yl]methylcarbamate

Following General Procedure A, 6.0 g (25 mmol) of [(5-butyl-1H-1,2,4-triazol-3-yl)methyl]carbamate was coupled with 16.4 g (25 mmol) of the alkylating reagent prepared in step 1 of Example 3. Silica gel chromatography (Waters Prep 500A) using ethyl acetate/hexane (2:3) gave 4.29 g (24%) of a faster moving isomer: NMR ($CDCl_3$) δ 0.94 (t, *J* = 8 Hz, 3H), 1.33-1.46 (m, 2H), 1.43 (s, 9H), 1.66-1.78 (m, 2H), 2.69 (t, *J* = 8 Hz, 2H), 4.26 (d, *J* = 8 Hz, 2H), 5.24 (s, 2H), 6.87-6.93 (m, 7H), 7.01 (d, *J* = 8 Hz, 2H), 7.11 (d, *J* = 8 Hz, 2H), 7.21-7.28 (m, 5H), 7.30-7.37 (m, 4H), 7.42-7.52 (m, 2H), 7.94 (dd, *J* = 8 and 2 Hz, 1H) and 9.74 g (54%) of a slower moving isomer: NMR ($CDCl_3$) δ 0.87 (t, *J* = 8 Hz, 3H), 1.24-1.36 (m, 2H), 1.44 (s, 9H), 1.57-1.69 (m, 2H), 2.58 (t, *J* = 8 Hz, 2H), 4.38 (d, *J* = 8 Hz, 2H), 5.12 (s, 2H), 6.91 (d, *J* = 8 Hz, 8H), 7.11 (d, *J* = 8 Hz, 2H), 7.21-7.28 (m, 6H), 7.30-7.37 (m, 4H), 7.42-7.52 (m, 2H), 7.91-7.96 (m, 1H). The faster moving isomer was dissolved in 30 ml of water/acetic acid (1:4) and stirred at ambient temperature overnight. The solvent was removed

in vacuo; the residue dissolved in dilute base and washed with toluene. The water layer was acidified to pH 3-4 and extracted with ethyl acetate. Recrystallization from acetonitrile gave 2.53 g (88%) of 1,1-dimethylethyl[3-butyl-[1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-5-yl]methylcarbamate as a colorless solid: mp 144-147°C; NMR ($CDCl_3$) δ 0.88 (t, *J* = 8 Hz, 3H), 1.22-1.45 (m, 2H), 1.36 (s, 9H), 1.54-1.66 (m, 2H), 2.56 (t, *J* = 8 Hz, 2H), 4.05 (d, *J* = 8 Hz, 2H), 5.38 (s, 2H), 5.50 (s, 1H), 7.06 (d, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 2H), 7.45 (dd, *J* = 8 and 2 Hz, 1H), 7.50-7.63 (m, 2H), 7.99 (d, *J* = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 495 (12), 395 (38), 367 (15), 207 (100), 178 (42); HRMS. Calc'd for M+Li: 495.2808. Found: 495.2771.

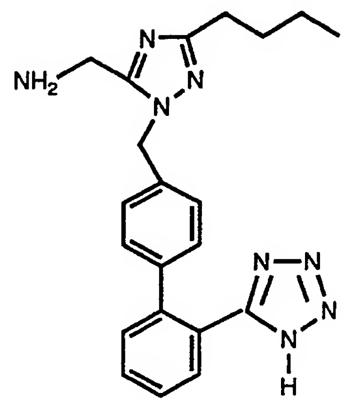
Example 35



1,1-dimethylethyl[5-butyl-[1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-3-yl]methylcarbamate

The slower moving isomer from Example 34 was dissolved in 70 ml of water/acetic acid (1:4) and stirred at ambient temperature overnight. The solvent was removed *in vacuo*; the residue dissolved in dilute base and washed with toluene. The water layer was acidified to pH 4 with 1N HCl and extracted with ethyl acetate. The ethyl acetate was dried ($MgSO_4$) and removed *in vacuo*. Lyophilization from acetonitrile/water gave 5.0 g (76%) of 1,1-dimethylethyl[5-butyl-[1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-3-yl]methylcarbamate as a colorless solid: NMR ($CDCl_3$) δ 0.77 (t, *J* = 8 Hz, 3H), 1.16-1.30 (m, 2H), 1.40 (s, 9H), 1.42-1.56 (m, 2H), 2.57 (t, *J* = 8 Hz, 2H), 4.12 (d, *J* = 8 Hz, 2H), 5.19 (s, 2H), 5.59 (s, 1H), 6.94 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H), 7.43 (dd, *J* = 8 and 2 Hz, 1H), 7.50-7.63 (m, 2H), 7.92 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 495 (29), 367 (38), 338 (21), 207 (100), 178 (48); HRMS. Calc'd for M+Li: 495.2808. Found: 495.2800.

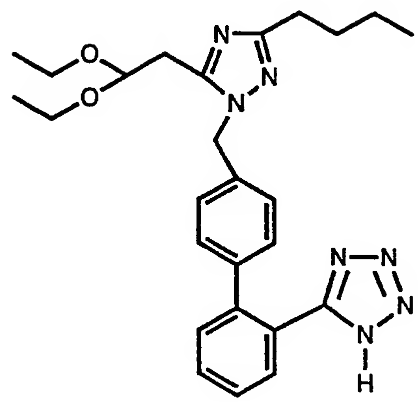
Example 36



<u>3-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-5-methanamine</u>

Under nitrogen, 219 mg (0.45 mmol) of 1,1-dimethylethyl [3-butyl-[1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-5-yl] methylcarbamate from Example 34 was suspended in 10 ml of 4N HCl in dioxane. After 30 minutes, 10 ml of methylene chloride was added. The mixture was stirred at ambient temperature overnight. The solvent was removed <u>in vacuo</u>. Lyophilization from acetonitrile/water gave 201 mg (100%) of 3-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-5-methanamine as the colorless hydrochloride salt: NMR ($CDCl_3$) δ 0.82 (t, *J* = 8 Hz, 3H), 1.21-1.35 (m, 2H), 1.59-1.72 (m, 2H), 2.72 (t, *J* = 8 Hz, 2H), 4.97 (s, 2H), 5.69 (s, 2H), 6.93 (d, *J* = 8 Hz, 2H), 7.23 (d, *J* = 8 Hz, 2H), 7.32 ((d, *J* = 8 Hz, 1H), 7.39 (dt, *J* = 8 and 2 Hz, 1H), 7.51 (dt, *J* = 8 and 2 Hz, 1H), 7.74 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 389 (55), 207 (100), 192 (39), 178 (26); HRMS. Calc'd for M+H: 389.2202. Found: 389.2170.

Example 37

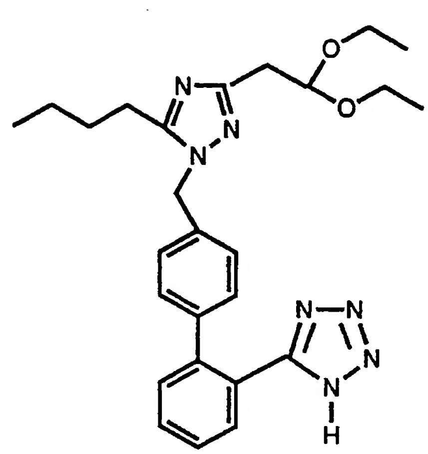


5-[4'-[[3-butyl-5-(2,2-diethyoxyethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following General Procedure A, 4.7 g (19.5 mmol) of 5-butyl-3-(2,2-diethoxyethyl)-1H-1,2,4-triazole was coupled with 19.5 mmol of the alkylating reagent prepared in step 1 of Example 3. Silica gel chromatography (Waters Prep 500A) using ethyl acetate/hexane (2:3) gave 5.98 g (43%) of a faster moving isomer: NMR ($CDCl_3$) δ 0.94 (t, *J* = 8 Hz, 3H), 1.13 (t, *J* = 8 Hz, 6H), 1.33-1.48 (m, 2H), 1.67-1.79 (m, 2H), 2.70 (t, *J* = 8 Hz, 2H), 2.94 (d, *J* = 8 Hz, 2H), 3.39-3.51 (m, 2H), 3.63-3.75 (m, 2H), 4.81 (t, *J* = 7 Hz, 1H), 5.22 (s, 2H), 6.87-6.98 (m, 8H), 7.09 (d, *J* = 8 Hz, 2H), 7.21-7.29 (m, 6H), 7.30-7.37 (m, 4H), 7.41-7.52 (m, 2H), 7.91-7.96 (m, 1H) and 6.3 g (45%) of a slower moving isomer: NMR ($CDCl_3$) δ 0.88 (t, *J* = 8 Hz, 3H), 1.15 (t, *J* = 7 Hz, 6H), 1.24-1.37 (m, 2H), 1.56-1.68 (m, 2H), 2.57 (t, *J* = 8 Hz, 2H), 3.06 (d, *J* = 7 Hz, 2H), 3.46-3.60 (m, 2H), 3.66-3.78 (m, 2H), 5.05 (t, *J* = 7 Hz, 1H), 5.14 (s, 2H), 6.87-6.95 (m, 8H), 7.10 (d, *J* = 8 Hz, 2H), 7.21-7.29 (m, 6H), 7.31-7.37 (m, 4H), 7.42-7.53 (m, 2H), 7.90-7.96 (m, 1H). The faster moving isomer was dissolved in 50 ml of acetic acid/water (4:1) and stirred at ambient

temperature for 3 days. The solvent was removed *in vacuo*; the residue dissolve in dilute base and washed with toluene. The water layer was cooled to 0 °C, acidified to pH 4-5 and extracted with ethyl acetate. Lyophilization from acetonitrile/water gave 3.8 g (98%) of 5-[4'-[[3-butyl-5-(2,2-diethyoxyethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: NMR ($CDCl_3$) δ 0.80 (t, *J* = 8 Hz, 3H), 1.10 (t, *J* = 8 Hz, 6H), 1.10-1.24 (m, 2H), 1.37-1.49 (m, 2H), 2.31 (t, *J* = 8 Hz, 2H), 2.66 (d, *J* = 7 Hz, 2H), 3.34-3.47 (m, 2H), 3.59-3.71 (m, 2H), 4.75 (t, *J* = 7 Hz, 1H), 5.28 (s, 2H), 6.88 (d, *J* = 8 Hz, 2H), 7.06 (d, *J* = 8 Hz, 2H), 7.46 (dd, *J* = 8 and 2 Hz, 1H), 7.55 (dt, *J* = 8 and 2 Hz, 1H), 7.62 (dt, *J* = 8 and 2 Hz, 1H), 7.91 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 476 (20), 430 (28), 356 (13), 235 (15), 207 (100), 192 (67); HRMS. Calc'd for M+H: 476.2773. Found: 476.2723.

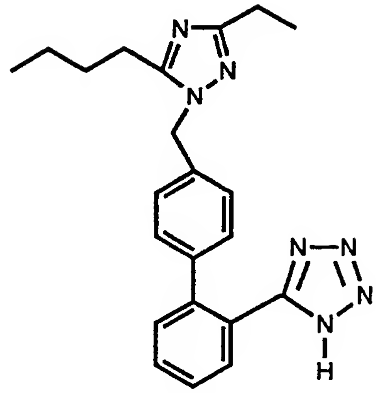
Example 38



5-[4'-[[5-butyl-3-(2,2-diethyoxyethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

The 6.2 g (8.6 mmol) of the slower moving isomer from Example 37 was dissolved in 50 ml of acetic acid/water (4:1) and stirred at ambient temperature for 3 days. The solvent was removed *in vacuo*; the residue dissolved in dilute base, and washed with toluene. The water layer was cooled to 0 °C, acidified with 1N HCl to pH 4-5, and extracted with ethyl acetate. Lyophilization from acetonitrile/water gave 3.7 g (92%) of 5-[4'-[[5-butyl-3-(2,2-diethyoxyethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as colorless solid: NMR ($CDCl_3$) δ 0.85 (t, *J* = 8 Hz, 3H), 1.09 (t, *J* = 8 Hz, 6H), 1.24-1.38 (m, 2H), 1.51-1.63 (m, 2H), 2.55 (t, *J* = 8 Hz, 2H), 2.75 (d, *J* = 7 Hz, 2H), 3.38-3.50 (m, 2H), 3.54-3.66 (m, 2H), 4.87 (t, *J* = 7 Hz, 1H), 5.19 (s, 2H), 6.99 (d, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 2H), 7.42 (dd, *J* = 8 and 2 Hz, 1H), 7.50-7.65 (m, 2H), 7.97 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 476 (3), 430 (28), 235 (10), 207 (100), 192 (61); HRMS. Calc'd for M+H: 476.2773. Found: 476.2760.

Example 39

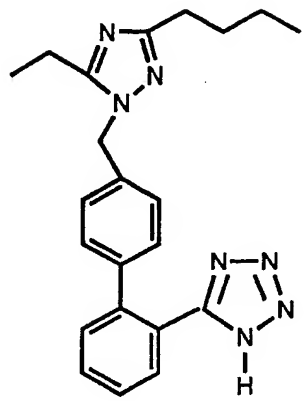


5-[4'-[(5-butyl-3-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following General Procedure A, 770 mg (5 mmol) of 5-butyl-3-ethyl-1H-1,2,4-triazole was coupled with 2.8 g (5 mmol) of the alkylating reagent prepared in step 1 of Example 3. Silica gel chromatography (Waters Prep-500A) using ethyl acetate/hexane (2:3) gave 2.24 g (72%) of a mixture of the two isomers which was dissolved in 30 ml of acetic acid/water (9:1) and stirred at ambient temperature for 4 days. The solvent was removed in vacuo; the residue dissolved in dilute base, and washed with toluene. The water layer was acidified to pH 4 and extracted with ethyl acetate. The extracts were combined, dried ($MgSO_4$) and concentrated in vacuo. Purification of a 600 mg sample of the isomeric product mixture by reverse phase chromatography (Waters Delta Prep-3000) using isocratic acetonitrile/water (25:75) (0.05% TFA) provided two isomers. The faster moving isomer was dissolved in dilute base, acidified, extracted with ethyl acetate, dried ($MgSO_4$) and the ethyl acetate removed in vacuo.

Lyophilization from acetonitrile/water gave 209 mg of 5-[4'-[(5-butyl-3-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: NMR ($CDCl_3$) δ 0.88 (t, *J*= 8 Hz, 3H), 1.33-1.40 (m, 2H), 1.38 (t, *J* = 8 Hz, 3H), 1.58-1.70 (m, 2H), 2.67-2.85 (m, 4H), 5.26 (s, 2H), 7.10 (s, 4H), 7.41 (dd, *J* = 8 and 2 Hz, 1H), 7.74-7.62 (m, 2H), 7.86 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 388 (58), 207 (100), 192 (35); HRMS. Calc'd for M+H: 388.2249. Found: 388.2218.

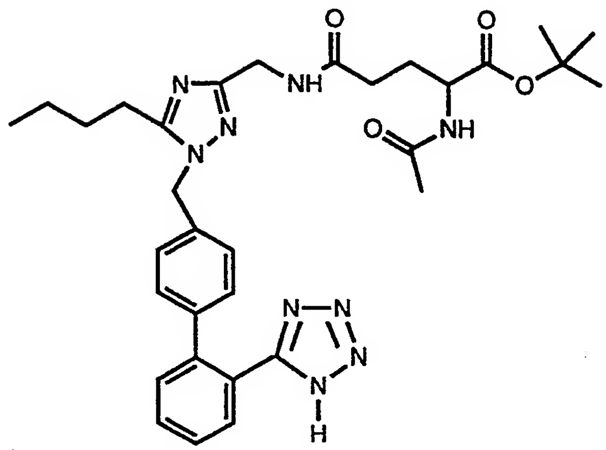
Example 40



5-[4'-[(3-butyl-5-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

The slower moving isomer from Example 39 was dissolved in dilute base, acidified to pH 3-4, extracted with ethyl acetate, dried ($MgSO_4$), and the ethyl acetate removed in vacuo. Lyophilization from acetonitrile/water gave 188 mg of 5-[4'-[(3-butyl-5-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: NMR ($CDCl_3$) δ 0.87 (t, *J* = 8 Hz, 3H), 1.16 (t, *J* = 8 Hz, 3H), 1.21-1.35 (m, 2H), 1.52-1.65 (m, 2H), 2.50 (t, *J* = 8 Hz, 2H), 2.67 (q, *J* = 8 Hz, 2H), 5.23 (s, 2H), 7.02 (d, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 2H), 7.43 (dd, *J* = 8 and 2 Hz, 1H), 7.50-7.65 (m, 2H), 7.89 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 388 (35), 207 (100), 192 (47); HRMS. Calc'd for M+H: 388.2249. Found: 388.2222.

Example 41

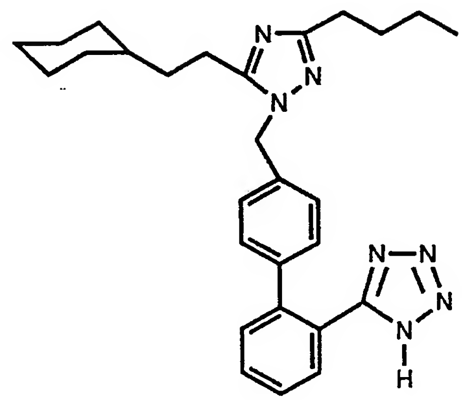


N2-acetyl-N-[[5-butyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1,2,4-triazol-3-yl]methyl]-L-glutamine, 1,1-dimethylethyl ester

Under nitrogen, 30 ml of TFA was added dropwise to a solution of 4.9 g (10 mmol) of 1,1dimethylethyl [5-butyl-[1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-3-yl]methyl]carbamate from Example 35 in 30 ml of methylene chloride at -10°C (methanol/ice). The mixture was allowed to warm to ambient temperature and stir overnight. The solvent was removed in vacuo giving the TFA salt of the free amine. The TFA salt was dissolved in 35 ml of anhydrous DMF along with 8.7 ml (50 mmol) of anhydrous diisopropyl ethyl amine and treated with 20 mmol of the symmetrical anhydride of N-Boc-γ-glutamic acid t-butyl ester in 55 ml of anhydrous DMF. The reaction was stirred at ambient temperature overnight. The DMF was removed in vacuo; the residue dissolved in ethyl acetate, washed with cold 1M K_2CO_3 and water. The ethyl acetate was dried ($MgSO_4$) and the solvent removed in vacuo. Under nitrogen, 30 ml of TFA was added dropwise to a solution of this material in 30 ml of methylene chloride at -10 °C

(methanol/ice). The reaction was allowed to warm to ambient temperature and stir overnight. The solvent was removed *in vacuo* giving the TFA salt of the free amine. The TFA salt was dissolved in 30 ml of water and cooled to 0 °C. The pH was adjusted to nine with 1M K_2CO_3 . The solution was cooled to 0 ° C, 0.94 ml (10 mmol) of acetic anhydride was added followed by 5 ml of 1M K_2CO_3, and the pH was adjusted to 9 with additional 1M K_2CO_3. At 30 minute intervals, this addition was repeated until 5 additions had been made. The pH was adjusted to 4 with 6N HCl and the solution extracted with ethyl acetate. The ethyl acetate was dried ($MgSO_4$) and removed *in vacuo*. Purification by silica gel chromatography (Waters Prep 500A) using isopropanol/acetic acid/chloroform (20:5:75) followed by lyophilization from acetonitrile/water gave 2.5 g (41%) of N2-acetyl-N-[[5-butyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1,2,4-triazol-3-yl]methyl]-L-glutamine, 1,1-dimethylethyl ester as a colorless solid: NMR ($CDCl_3$) δ 0.89 (t, *J* = 8 Hz, 3H), 1.27-1.41 (m, 2H), 1.52-1.71 (m, 2H), 1.56 (s, 9H), 2.00 (s, 3H), 2.05-2.29 (m, 2H), 2.31-2.55 (m, 2H), 2.73 (t, *J* = 8 Hz, 2H), 4.48-4.58 (m, 3H), 5.24 (s, 2H), 7.09 (d, *J* = 8 Hz, 2H), 7.17 (d, *J* = 8 Hz, 2H), 7.36-7.42 (m, 1H), 7.44-7.55 (m, 2H), 7.90 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 616 (20), 263 (23), 235 (26), 207 (100); HRMS. Calc'd for M+H: 616.3360. Found: 616.3353.

Example 42

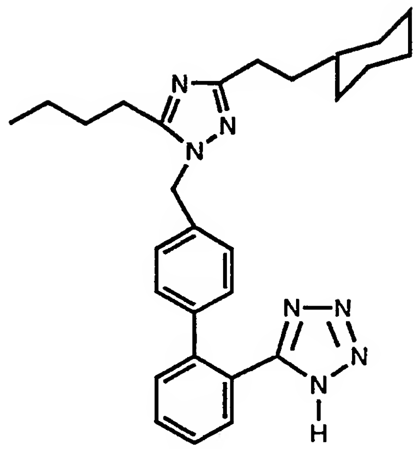


5-[4'-[[3-butyl-5-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following General Procedure A, 1.2 g (5 mmol) of 5-butyl-3-(2-cyclohexylethyl)-1H-1,2,4-triazole was coupled with 5 mmol of the alkylating reagent prepared in step 1 of Example 3. Silica gel chromatography (Waters Prep 500A) using ethyl acetate/hexane (1:3) gave 3.6 g (100%) of a mixture of the two isomers which was dissolved in 50 ml of acetic acid/water (9:1) and stirred at ambient temperature overnight. The solvent was removed in vacuo; the residue dissolved in dilute base, acidified and washed with ethyl acetate. The ethyl acetate was removed in vacuo. Purification of a small sample of the isomer product mixture by reverse phase chromatography (Water Delta Prep-3000) using isocratic acetonitrile/water (41:59) (0.05% TFA) provided two isomers. The faster moving isomer was dissolved in dilute base, acidified to pH 3-4, extracted with ethyl acetate, dried ($MgSO_4$) and the ethyl acetate removed in vacuo. Lyophilization from acetonitrile/water gave 58 mg of 5-[4'-[[3-butyl-5-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: NMR ($CDCl_3$) δ 0.78-0.95 (m, 5H), 1.07-1.40 (m, 6H), 1.48-1.74 (m, 9H), 2.66 (t, J =

8 Hz, 2H), 2.78 (t, J = 8 Hz, 2H), 5.24 (s, 2H), 7.10 (q, J = 8 Hz, 4H), 7.41 (dd, J = 8 and 2 Hz, 1H), 7.48-7.63 (m, 2H), 7.89 (dd, J = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 470 (45), 236 (35), 207 (100), 192 (33); HRMS. Calc'd for M+H: 470.3032. Found: 470.2990.

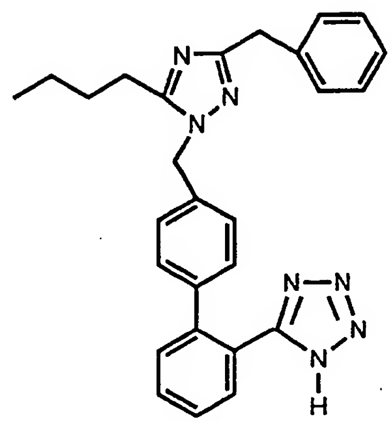
Example 43



5-[4'-[[5-butyl-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

The slower moving isomer from Example 42 was dissolved in dilute base, acidified to pH 3-4, extracted with ethyl acetate, dried ($MgSO_4$), and the ethyl acetate removed *in vacuo*. Lyophilization from acetonitrile/water gave 29 mg of 5-[4'-[[5-butyl-3-(2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: NMR ($CDCl_3$) δ 0.95-1.00 (m, 5H), 1.10-1.43 (m, 6H), 1.59-1.77 (m, 9H), 2.83 (t, *J* = 8 Hz, 2H), 2.92 (t, *J* = 8 Hz, 2H), 5.31 (s, 2H), 7.10-7.18 (m, 4H), 7.40 (dd, *J* = 8 and 2 Hz, 1H), 7.47-7.61 (m, 2H), 7.89 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 470 (35), 236 (33), 207 (100), 192 (33); HRMS. Calc'd for M+H: 470.3032. Found: 470.2994.

Example 44

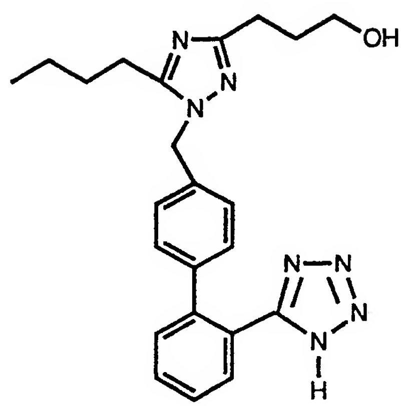


5-[4'-[[5-butyl-3-(phenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Under nitrogen, 0.74 g (2.2 mmol) of N2-[4-[(2-cyanophenyl)phenyl]methyl] phenyl acetic acid hydrazide was dissolved in 5 ml of absolute ethanol and treated with 0.28 g (2.2 mmol) of ethyl iminovalerate. The reaction was stirred at relux for 3 days. The solvent was removed *in vacuo*, 5 ml of xylene was added and the reaction stirred at reflux under nitrogen for an additional 3 days. The solvent was removed *in vacuo*. Purification by silica gel chromatography (Chromatatron, 4 mm plate) using a step gradient of ethyl acetate/chloroform gave 410 g (31%) of 5-[4'-[[5-butyl-3-(phenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl-2-yl]nitrile: NMR ($CDCl_3$) δ 0.88 (t, *J* = 8 Hz, 3H), 1.27-1.41 (m, 2H), 1.59-1.72 (m, 2H), 2.67 (t, *J* = 8 Hz, 2H), 4.06 (s, 2H), 5.30 (s, 2H), 7.14-7.37 (m, 8H), 7.39-7.50 (m, 3H), 7.53 (dt, *J* = 8 and 2 Hz, 1H), 7.75 (dd, *J* = 8 and 2 Hz, 1H). Under nitrogen, 230 mg (1.13 mmol) of trimethyl tin azide was added to a solution of the nitrile in 5 ml of xylene. The reaction was stirred at reflux for 3 days. The solvent was removed *in vacuo* and

the residue dissolved in 10 ml of acetic acid/water (9:1) and stirred at ambient temperature overnight. The solvent was removed *in vacuo*. Reverse phase chromatography (Delta Prep 3000) using acetonitrile/water (35-45:65-55) gave the TFA salt. The salt was dissolved in dilute base, acidified to pH 3-4, extracted with ethyl acetate, dried ($MgSO_4$) and the ethyl acetate removed *in vacuo*. Lyophilization from acetonitrile/water gave 182 mg (45%) of 5-[4'-[[5-butyl-3-(phenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: NMR ($CDCl_3$) δ 0.84 (t, *J* = 8 Hz, 3H), 1.22-1.36 (m, 2H), 1.51-1.64 (m, 2H), 2.59 (t, *J* = 8 Hz, 2H), 3.85 (s, 2H), 5.20 (s, 2H), 7.02 (d, *J* = 8 Hz, 2H), 7.14 (d, *J* = 8 Hz, 2H), 7.17-7.28 (m, 5H), 7.43 (dd, *J* = 8 and 2 Hz, 1H), 7.51-7.65 (m, 2H), 7.96 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 450 (56), 207 (100), 192 (30), 178 (22); HRMS. Calc'd for M+H: 450.2406. Found: 450.2434.

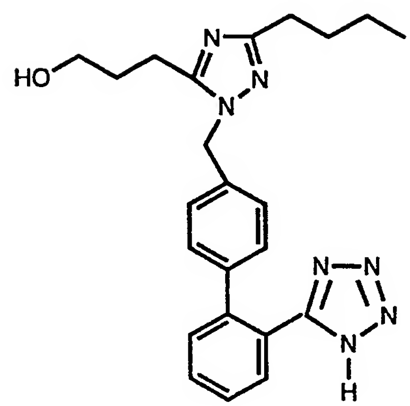
Example 45



5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-3-propanol

Following General Procedure A, 920 mg (5.0 mmol) of 5-butyl-1H-1,2,4-triazole-3-propanol was coupled with 5.0 mmol of the alkylating reagent prepared in step 1 of Example 3. Silica gel chromatography (Waters Prep 500A) using isopropanol/chloroform (5:95) gave a mixture of the two pure isomers which was dissolved in 40 ml acetic acid/water (9:1) and stirred at ambient temperature for 3 days. The solvent was removed in vacuo. Purification of an aliquot by reverse phase chromatography (Waters Delta Prep 3000) using acetonitrile/water (26:74) (0.05% TFA) provided two isomers. Lyophilization of the faster moving isomer from acetonitrile/ water gave 124 mg of 5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-3-propanol as the colorless FTA salt: NMR ($CDCl_3$) δ 0.71 (t, J = 8 Hz, 3H), 1.10-1.24 (m, 2H), 1.42-1.54 (m, 2H), 1.70-1.81 (m, 2H), 2.49 (t, J = 8 Hz, 2H), 2.60 (t, J = 8 Hz, 2H), 3.46 (t, J = 6 Hz, 2H), 5.02 (s, 2H), 6.92 (q, J = 8 Hz, 4H), 7.24-7.34 (m, 2H), 7.40 (dt, J = 8 and 2 Hz, 1H), 7.52 (dd, J = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 418 (100), 207 (48), 184 (10); HRMS. Calc'd for M+H: 418.2355. Found: 418.2370.

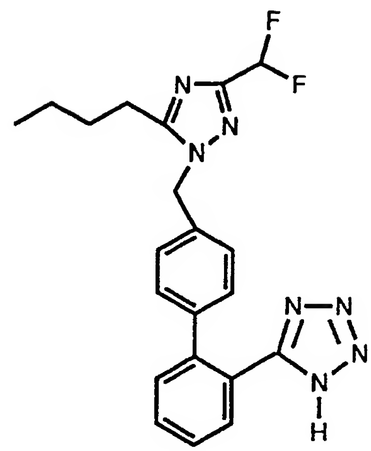
Example 46



3-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-1ylmethyl]-1H-1,2,4-triazole-5-propanol

Lyophilization of the slower moving isomer from Example 45 gave 114 mg of 3-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-1ylmethyl]-1H-1,2,4-triazole-5-propanol as the colorless TFA salt: NMR ($CDCl_3$) δ 0.75 (t, *J* = 8 Hz, 3H), 1.13-1.27 (m, 2H), 1.48-1.60 (m, 2H), 1.64-1.75 (m, 2H), 2.52 (t, *J* = 8 Hz, 2H), 2.66 (t, *J* = 8 Hz, 2H), 3.39 (t, *J* = 6 Hz, 2H), 5.12 (s, 2H), 6.94 (s, 4H), 7.25-7.35 (m, 2H), 7.40 (dt, *J* = 8 and 2 Hz, 1H), 7.52 (d, *J* = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 418 (100), 207 (30); HRMS. Calc'd for M+H: 418.2355. Found: 418.2344.

Example 47

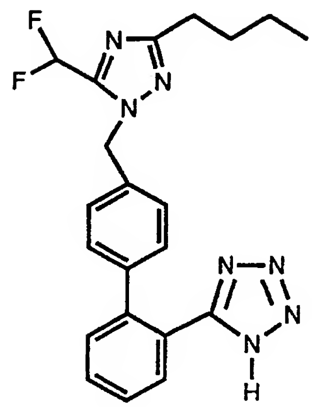


<u>5-[4'-[[5-butyl-3-(difluoromethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole</u>

Following General Procedure A, 470 mg (2.7 mmol) of 5-butyl-3-(difluoromethyl)-1H-1,2,4-triazole was coupled with 2.7 mmol of the alkylating reagent prepared in step 1 of Example 3. Purification by reverse phase chromatography (Waters Delta Prep 3000) using acetonitrile/water (36:64) (0.05% TFA) gave two isomers. The faster moving isomer was dissolved in dilute base, acidified to pH 3-4, extracted with ethyl acetate, dried ($MgSO_4$), and the ethyl acetate removed <u>in vacuo</u>. Lyophilization from acetonitrile/water gave 471 mg (27%) of 5-[4'-[[5-butyl-3-(difluoromethyl)-1H-1,2,4-triazol-1-yl]methyl][1.1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: NMR ($CDCl_3$) δ 0.88 (t, *J* = 8 Hz, 3H), 1.28-1.43 (m, 2H), 1.60-1.73 (m, 2H), 2.72 (t, *J* = 8 Hz, 2H), 5.32 (s, 2H), 6.61 (t, *J* = 54 Hz, 1H), 7.12 (d, *J* = 8 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H), 7.42 (dd, *J* = 8 and 2 Hz, 1H), 7.51-7.65 (m, 2H), 8.00 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 410 (45), 235 (55), 207 (100), 192 (57); HRMS. Calc'd for M+H: 410.1905. Found:

410.1903.

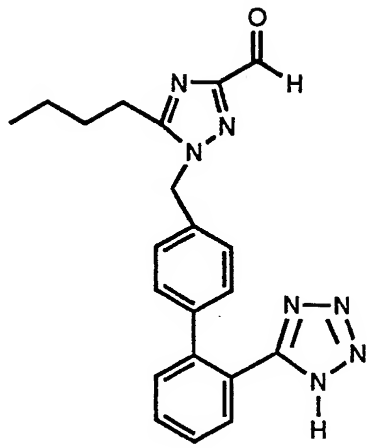
Example 48



5-[4'-[[3-butyl-5-(difluoromethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

The slower moving isomer from Example 47 was dissolved in dilute base, acidified, extracted with ethyl acetate, dried ($MgSO_4$), and the ethyl acetate removed *in vacuo*. Lyophilization from acetonitrile/water gave 104 mg (6%) of 5-[4'-[[3-butyl-5-(difluoromethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: NMR ($CDCl_3$) δ 0.91 (t, *J* = 8 Hz, 3H), 1.25-1.41 (m, 2H), 1.60-1.73 (m, 2H), 2.64 (t, *J* = 8 Hz, 2H), 5.43 (s, 2H), 6.81 (t, *J* = 52 Hz, 1H), 7.20 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H), 7.43 (dd, *J* = 8 and 2 Hz, 1H), 7.52-7.65 (m, 2H), 8.10 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 410 (87), 235 (100), 207 (83); HRMS. Calc'd for M+H: 410.1905. Found: 410.1903.

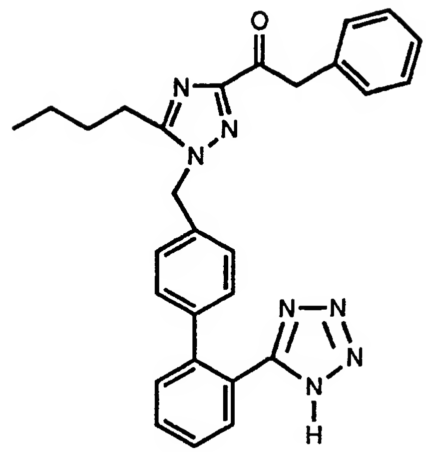
Example 49



5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-3-carboxaldehyde

A 92 mg sample of 5-[4'-[[5-butyl-3-(dimethoxymethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole from Example 24 was dissolved in 20 ml of ethanol and 2 ml of 3N HCl. The reaction was stirred at ambient temperature for 3 days. The solvent was removed in vacuo. Lyophilization from acetonitrile/water gave 70 mg (81%) of 5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-3-carboxaldehyde as the colorless hydrochloride salt: NMR ($CDCl_3$) δ 0.89 (t, *J* = 8 Hz, 3H), 1.30-1.44 (m, 2H), 1.66-1.78 (m, 2H), 2.78 (t, *J* = 8 Hz, 2H), 5.38 (s, 2H), 7.17 (q, *J* = 8 Hz, 4H), 7.40 (d, *J* = 8 Hz, 1H), 7.50-7.64 (m, 2H), 8.02 (d, *J* = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 388 (36), 235 (42), 207 (100), 192 (50); HRMS. Calc'd for M+Li: 395.2046. Found: 395.2049.

Example 50

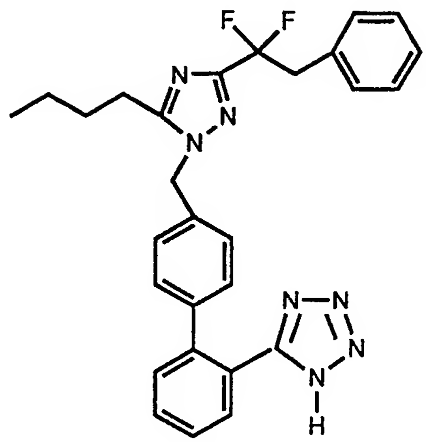


5-[4'-[[5-butyl-3-(phenylacetyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Under nitrogen, 7.3 mmol of sec-butyl lithium was added dropwise to 2.0 g (6.1 mmol) of the Sem-protected 5-butyl-3-(dimethoxymethyl)-1H-1,2,4-triazole from Example 30 in 100 ml of anhydrous THF at -78 °C. The reaction was stirred for 1 h and then quenched with 0.87 ml (7.3 mmol) of benzyl bromide. The reaction was allowed to warm to ambient temperature and stir overnight. The THF was removed *in vacuo*; the residue dissolved in methylene chloride, washed with water and dried ($MgSO_4$). The methylene chloride was removed *in vacuo*. The residue was dissolved in 10 ml of ethanol and 10 ml of 3M HCl and stirred at reflux for 2.5 h. The solvents were removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with saturated sodium bicarbonate solution, and dried ($MgSO_4$). Silica gel chromatography (Waters Prep 500A) using ethyl acetate/hexane (35:65) gave 460 mg (31%) of 5-butyl-3-(phenylacetyl)-1H-1,2,4-triazole: NMR ($CDCl_3$) δ 0.92 (t, *J* = 8 Hz, 3H), 1.31-1.55 (m, 2H), 1.70-1.83 (m, 2H), 2.88 (t, *J* = 8 Hz, 2H), 4.39 (s, 2H), 7.21-7.38 (m,

5H). Following General Procedure A, 440 mg (1.8 mmol) of this material was reacted with 1.8 mmol of the alkylating reagent prepared in step 1 of Example 3. The crude product was dissolved in 10 ml of acetic acid/water (9:1) and stirred at ambient temperature for 4 days. The solvent was removed *in vacuo*; the residue dissolved in dilute base and washed with toluene. The water was acidified and extracted with ethyl acetate. Purification by reverse phase chromatography (Waters Delta Prep 3000) using acetonitrile/water (45:55) gave 50 mg (5%) of 5-[4'-[[5-butyl-3-(phenylacetyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as the colorless TFA salt: NMR ($DMSO-d_6$) δ 0.86 (t, *J* = 8 Hz, 3H), 1.23-1.38 (m, 2H), 1.52-1.65 (m, 2H), 2.80 (t, *J* = 8 Hz, 2H), 4.32 (s, 2H), 5.52 (s, 2H), 7.11 (d, *J* = 8 Hz, 2H), 7.19 (d, *J* = 8 Hz, 2H), 7.23-7.35 (m, 5H), 7.52-7.63 (m, 2H), 7.65-7.74 (m, 2H); MS (FAB) m/e (rel intensity) 478 (100), 244 (8), 235 (8), 207 (34), 192 (12); HRMS. Calc'd for M+H: 478.2355. Found: 478.2414.

Example 51



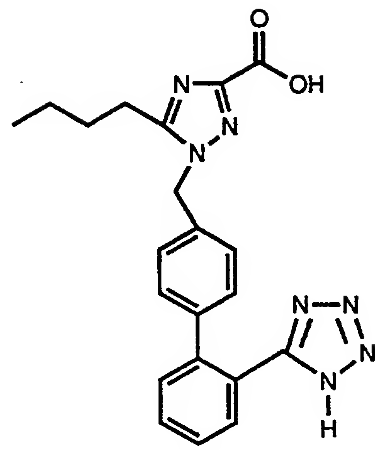
5-[4'-[[5-butyl-3-(1,1-difluoro-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-1-yl]-1H-tetrazole

Under nitrogen, 8.5 g (48 mmol) of 5-butyl-3-(difluoromethyl)-1H-1,2,4-triazole from Example 47 was added in portions to 53 mmol of sodium hydride in 85 ml of anhydrous THF; stirring was continued for 1 h. The anion solution was cooled to 0 °C and treated dropwise with 8.9 ml (50 mmol) of Sem-Cl. The reaction was allowed to warm to ambient temperature and stir overnight. The THF was removed *in vacuo*; the residue dissolved in methylene chloride, washed with water, and dried ($MgSO_4$). Purification by silica gel chromatography (Waters Prep 500A) using ethyl acetate/hexane (1:9) gave 4.9 g 34% of the Sem-protected triazole as an oil: NMR ($CDCl_3$) δ -0.04 (s, 9H), 0.86-0.95 (m, 5H), 1.39-1.43 (m, 2H), 1.65-1.76 (m, 2H), 2.71 (t, *J* = 8 Hz, 2H), 3.62 (t, *J* = 8 Hz, 2H), 5.53 (s, 2H), 6.82 (t, *J* = 52 Hz, 1H). Under nitrogen, 14.2 mmol of sec-butyllithium was added dropwise to 3.6 g (11.8 mmol) of the Sem-protected triazole in 200 ml of anhydrous THF at -78 °C. The reaction was allowed to stir for 1 h prior to the addition of 1.7 ml (14.2 mmol) of

benzyl bromide. After stirring at -78 °C for 2 h, the reaction was allowed to warm to ambient temperature and stir overnight. The solvent was removed in vacuo; the residue dissolved in methylene chloride, washed with water, and dried ($MgSO_4$). Silica gel chromatography (Waters Prep 500A) using ethyl acetate/hexane (5:95) gave 600 mg (10%) of the Sem protected 5-butyl-3-(1,1-difluoro-2-phenylethyl)-1H-1,2,4-triazole: NMR ($CDCl_3$) δ -0.04 (s, 9H), 0.85 (t, J = 8Hz, 2H), 0.94 (t, J = 8 Hz, 3H), 1.30-1.44 (m, 2H), 1.67-1.79 (m, 2H), 2.73 (t, J = 8 Hz, 2H), 3.54 (t, J = 8 Hz, 2H), 3.70 (t, J = 16 Hz, 2H), 5.34 (s, 2H), 7.21-7.31 (m, 5H). The Sem protected triazole was dissolved in 5 ml of ethanol and 5 ml of 3M HCl and allowed to stir at reflux for 3 h. The ethanol was removed in vacuo and the pH adjusted to nine with dilute sodium hydroxide. The resulting solution was extracted with methylene chloride; the extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to provide 5-butyl-3-(1,1-difluoro-2-phenethyl-1H-1,2,4-triazole. Following General Procedure A, 1.4 mmol of this material was coupled with 1.4 mmol of the alkylating reagent prepared in step 1 of Example 3. The crude product was dissolved in 10 mL of acetic acid/water (9:1) and stirred at ambient temperature for 3 days. The solvent was removed in vacuo; the residue dissolved in dilute base and washed with toluene. The water was acidified to pH 3-4, extracted with ethyl acetate, and dried ($MgSO_4$). Purification by reverse phase chromatography (Waters Delta Prep 3000) using acetonitrile/water (47:53) (0.05% TFA) gave the TFA salt. The salt was dissolved in dilute base, acidified to pH 3-4, extracted with ethyl acetate, and dried ($MgSO_4$). Lyophilization from acetonitrile/water gave 290 mg (42%) of 5-[4'-[[5-butyl-3-(1,1-difluoro-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-1-yl]-1H-tetrazole: NMR ($CDCl_3$) δ 0.86 (t, J = 8 Hz, 3H), 1.21-1.36 (m, 2H), 1.54-1.68 (m, 2H), 2.64 (t, J = 8 Hz, 2H), 3.57 (t, J = 16 Hz, 2H), 5.23 (s, 2H), 6.92 (d, J = 8 Hz, 2H), 7.10 (d, J =

8 Hz, 2H), 7.16-7.25 (m, 5H), 7.39 (dd, J = 8 and 2 Hz, 1H), 7.50-7.65 (m, 2H), 7.99 (dd, J = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 500(100), 266 (6), 235 (8), 207 (25), 192 (8); HRMS. Calc'd for M+H: 500.2374. Found: 500.2358.

Example 52

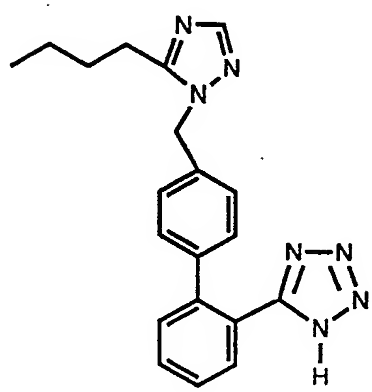


5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-3-carboxylic acid

A 3.36 g (7.1 mmol) sample of 5-[4'-[[5-butyl-3-(2,2-diethyoxyethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole from Example 38 was dissolved in 15 ml of ethanol and 15 ml of 3M HCl. The reaction was stirred at ambient temperature overnight and then at reflux for 2 h. The solvent was removed *in vacuo*, the residue dissolved in 15 ml of THF and 15 ml of 3M HCl and stirred for 3 days at ambient temperature. The solvent was removed *in vacuo*; the residue dissolved in dilute base, acidified and extracted with ethyl acetate and methylene chloride. The solvents were combined and dried ($MgSO_4$). The solvents were removed *in vacuo*. The residue was dissolved in 70 ml of acetone and 35 ml of water. Potassium permanganate was added in 4 equal portions of 190 mg after each preceeding portion had reacted. The mixture was filtered through celite and the solvent removed *in vacuo*. Purification by reverse phase chromatography (Waters Delta Prep 3000) gave 88 mg (7%) of 5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-3-carboxylic acid

as the colorless TFA salt after lyophilization from acetonitrile/water: NMR (DMSO-d_6) δ 0.85 (t, *J* = 8 Hz, 3H), 1.23-1.38 (m, 2H), 1.52-1.62 (m, 2H), 2.78 (t, *J* = 8 Hz, 2H), 5.46 (s, 2H), 7.13 (q, *J* = 8 Hz, 4H), 7.51-7.62 (m, 2H), 7.64-7.73 (m, 2H); MS (FAB) m/e (rel intensity) 404 (100), 235 (20), 207 (91), 192 (24); HRMS. Calc'd for M+H: 404.1835. Found: 404.1882.

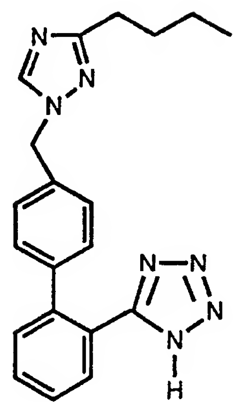
Example 53



5-[4'-[(5-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following general procedure A , 630 mg (5 mmol) of 3-butyl-1H-1,2,4-triazole was reacted with 5 mmol of the alkylating reagent prepared in step 1 of Example 3 to give 2.3 g (76%) of a mixture of the two isomers. Deprotection of the faster isomer provided 5-[4'-[(5-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]1H-tetrazole: NMR ($CDCl_3$) δ 0.87 (t, J = 8 Hz, 3H), 1.35-1.41 (m, 2H), 1.59-1.72 (m, 2H), 2.72 (t, J = 8 Hz, 2H), 5.30 (s, 2H), 7.09 (d, J = 8 Hz, 2H), 7.17 (d, J = 8 Hz, 2H), 7.44 (dd, J = 8 and 2 Hz, 1H), 7.52-7.66 (m, 2H), 7.72 (s, 1H), 8.01 (dd, J = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 360 (88), 235 (20), 207 (100),192 (31), 178 (22); HRMS. Calc'd for M+H: 360.1936. Found: 360.1938.

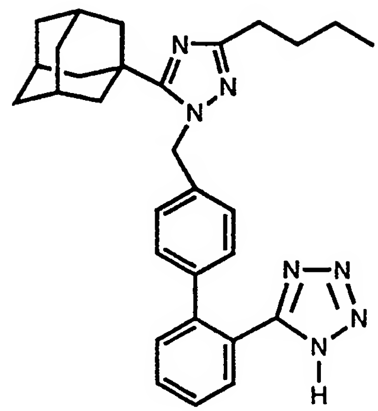
Example 54



5-[4'-[(3-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

The slower moving isomer from Example 53 was deprotected to provide 5-[4'-[(3-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole: NMR ($CDCl_3$) δ 0.74 (t, *J* = 8 Hz, 3H), 1.19-1.33 (m, 2H), 1.51-1.63 (m, 2H), 2.55 (t, *J* = 8 Hz, 2H), 5.23 (s, 2H), 7.10 (q, *J* = 8 Hz, 4H), 7.44 (dd, *J* = 8 and 2 Hz, 1H), 7.50-7.64 (m, 2H), 7.92 (dd, *J* = 8 and 2 Hz, 1H), 8.02 (s, 1H); MS (FAB) m/e (rel intensity) 360 (84), 135 (18), 207 (100), 192 (26), 178 (16), 126 (22); HRMS. Calc'd for M+H: 360.1936. Found: 360.1971.

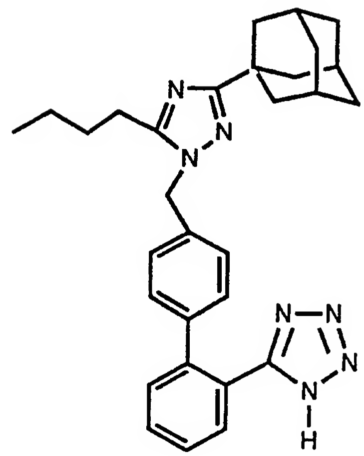
Example 55



5-[4' [[3-butyl-5-(tricyclo[3.3.1$^{3.7}$]dec-1-yl]-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following general procedure A, 1.3 g (5.0 mmol) of 5-butyl-3-adamantyl-1H-1,2,4-triazole was reacted with 5.0 mmol of the alkylating reagent prepared in step 1 of Example 3 to give 2.94 g (72%) of a mixture of the two isomers. Deprotection of the faster moving isomer provided 5-[4'-[[3-butyl-5-(tricyclo[3.3.1$^{3.7}$]dec-1-yl]-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole: NMR ($CDCl_3$) δ 0.90 (t, *J* = 8 Hz, 3H), 1.27-1.41 (m, 2H), 1.42-1.55 (m, 3H), 1.58-1.73 (m, 5H), 1.76-1.91 (m, 9H), 2.28-2.43 (m, 2H), 5.42 (s, 2H), 6.72-6.83 (m, 2H), 7.07 (d, *J* = 8 Hz, 2H), 7.45-7.66 (m, 3H), 7.88 (t, *J* = 8 Hz, 1H);MS (FAB) m/e (rel intensity) 494 (100), 260 (37), 207 (74), 178 (22); HRMS. Calc'd for M+H: 494.3032. Found: 494.3014.

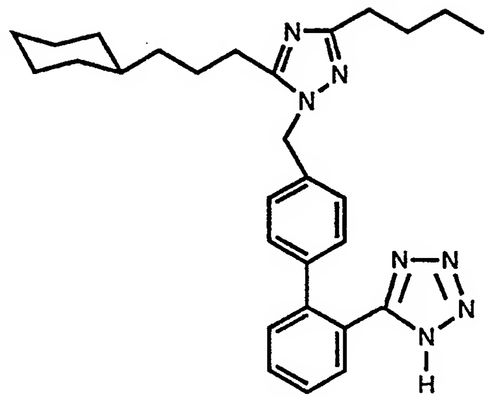
Example 56



5-[4'-[[5-butyl-3-(tricyclo[3.3.1.1$^{3.7}$]dec-1-yl]-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

The slower moving isomer from Example 55 was deprotected to provide 5-[4'-[[5-butyl-3-(tricyclo[3.3.1.1$^{3.7}$]dec-1-yl]-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole: NMR ($CDCl_3$) δ 0.87 (t, *J* = 8 Hz, 3H), 1.31-1.47 (m, 2H), 1.52-1.71 (m, 9H), 1.78 (s, 7H), 1.88 (s, 3H), 2.20-2.35 (m, 2H), 5.22 (s, 2H), 6.87 (d, *J* = 8 Hz, 2H), 7.13 (d, *J* = 8 Hz, 2H), 7.42 (dd, *J* = 8 and 2 Hz, 1H), 7.49-7.63 (m, 2H), 7.93 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 494 (73), 451 (10), 260 (24), 207 (66), 178 (21); HRMS. Calc'd for M+H: 494.3032. Found: 494.3026.

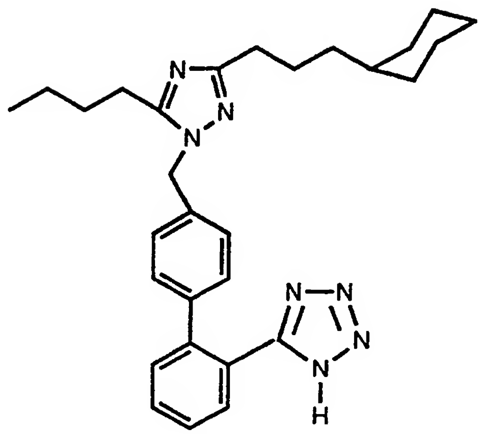
Example 57



5-[4'-[[3-butyl-5-(3-cyclohexylpropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following general procedure A, 1.25 g (5 mmol) of 5-butyl-3-(3-cyclohexylpropyl)-1H-1,2,4-triazole was reacted with 5 mmol of the alkylating reagent prepared in step 1 of Example 3 to give 3.1 g (85%) of a mixture of the two isomers. Deprotection of the faster moving isomer provided 5-[4'-[[3-butyl-5-(3-cyclohexylpropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole: NMR ($CDCl_3$) δ 0.73-0.92 (m, 2H), 0.87 (t, *J* = 8 Hz, 3H), 1.06-1.21 (m, 6H), 1.22-1.36 (m, 2H), 1.53-1.71 (m, 9H), 2.51 (t, *J* = 8 Hz, 2H), 2.61 (t, *J* = 8 Hz, 2H), 5.22 (s, 2H), 7.01 (d, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 2H), 7.42 (dd, *J* = 8 and 2 Hz, 1H), 7.51-7.64 (m, 2H), 7.94 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 484 (83), 250 (38), 207 (100), 178 (25); HRMS. Calc'd for M+H: 484.3189. Found: 484.3223.

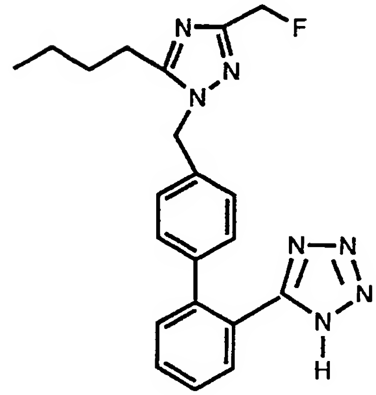
Example 58



5-[4'-[[5-butyl-3-(3-cyclohexylpropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

The slower moving isomer from Example 57 was deprotected to provide 5-[4'-[[5-butyl-3-(3-cyclohexylpropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole: NMR ($CDCl_3$) δ 0.74-0.90 (m, 2H), 0.83 (t, J = 8 Hz, 3H), 1.05-1.22 (m, 6H), 1.23-1.35 (m, 2H), 1.50-1.70 (m, 9H), 2.40 (t, J = 8 Hz, 2H), 2.57 (t, J = 8 Hz, 2H), 5.20 (s, 2H), 6.96 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 7.43 (dd, J = 8 and 2 Hz, 2H), 7.50-7.64 (m, 2H), 7.92 (dd, J = 8 and 2 Hz, 2H); MS (FAB) m/e (rel intensity) 484 (65), 250 (26), 207 (100), 178 (18); HRMS. Calc'd for M+H: 484.3189. Found: 484.3181.

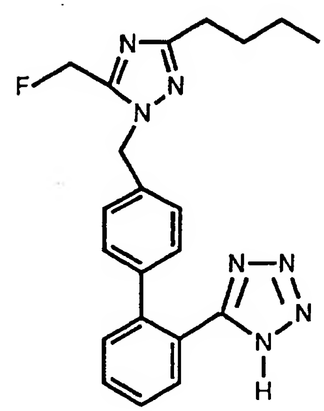
Example 59



5-[4'-[[5-butyl-3-(fluoromethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following general procedure A, 790 mg (5.0 mmol) of 5-butyl-3-(fluoromethyl)-1H-1,2,4-triazole was reacted with 5 mmol of the alkylating reagent prepared in step 1 of Example 3 to give 1.3 g (42%) of a mixture of the two isomers. Deprotection of the faster moving isomer provided 5-[4'-[[5-butyl-3-(fluoromethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole: NMR ($CDCl_3$) δ 0.86 (t, *J* = 8 Hz, 3H), 1.26-1.40 (m, 2H), 1.56-1.69 (m, 2H), 2.67 (t, *J* = 8 Hz, 2H), 5.16 (s, 1H), 5.27 (s, 2H), 5.32 (s, 1H), 7.06 (d, *J* = 8 Hz, 2H), 7.16 (d, *J* = 8 Hz, 2H), 7.43 (dd, *J* = 8 and 2 Hz, 1H), 7.52-7.65 (m, 2H), 7.99 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 392 (100), 235 (22), 207 (66), 192 (18), 178 (14); HRMS. Calc'd for M+H: 392.1999. Found: 392.1932.

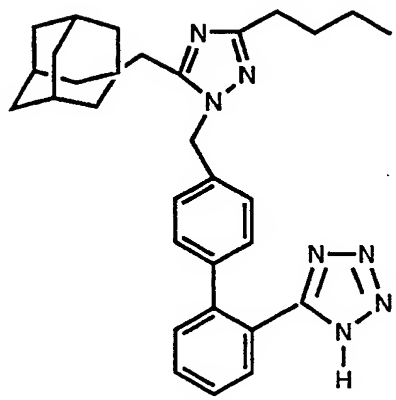
Example 60



5-[4'-[[3-butyl-5-(fluoromethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

The slower moving isomer from Example 59 was deprotected to provide 5-[4'-[[3-butyl-5-(fluoromethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole: NMR ($CDCl_3$) δ 0.89 (t, *J* = 8 Hz, 3H), 1.24-1.40 (m, 2H), 1.59 (m, 2H), 2.65 (t, *J* = 8 Hz, 2H), 5.38 (s, 3H), 5.55 (s, 1H), 7.21 (s, 4H), 7.43 (d, *J* = 8 Hz, 1H), 7.51-7.65 (m, 2H), 8.05 (d, *J* = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 392 (90), 235 (56), 207 (100), 192 (51), 178 (24); HRMS. Calc'd for M+H: 392.1999. Found: 392.1944.

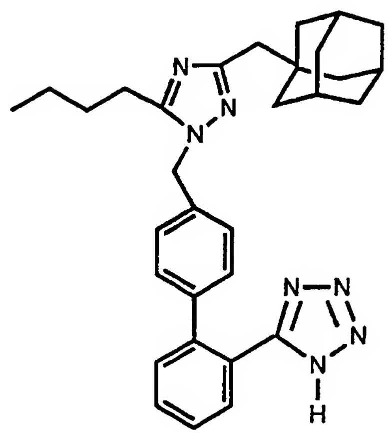
Example 61



5-[4'-[[3-butyl-5-(tricyclo[$3.3.1.1^{3.7}$]dec-1-ylmethyl]-1H-1,2,4-triazole-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following general procedure A, 1.4 g (5.0 mmol) of 5-butyl-3-adamantyl-1H-1,2,4-triazole was reacted with 5.0 mmol of the alkylating reagent prepared in step 1 of Example 3 to give a mixture of the two isomers. Deprotection of the faster moving isomer provided 5-[4'-[[3-butyl-5-(tricyclo[$3.3.1.1^{3.7}$]dec-1-ylmethyl]-1H-1,2,4-triazole-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole: NMR ($CDCl_3$) δ 0.84 (t, *J* = 8 Hz, 3H), 1.16-1.30 (m, 2H), 1.41 (s, 6H), 1.44-1.56 (m, 5H), 1.65 (d, *J* = 12 Hz, 3H), 1.92 (s, 3H), 2.18 (s, 2H), 2.30 (t, *J* = 8 Hz, 2H), 5.18 (s, 2H), 6.79 (d, *J* = 8 Hz, 2H), 7.01 (d, *J* = 8 Hz, 2H), 7.46 (d, *J* = 8 Hz, 1H), 7.52 (m, 2H), 7.85 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 508 (45), 274 (25), 207 (100), 192 (31); HRMS. Calc'd for M+H: 508.3189. Found: 508.3162.

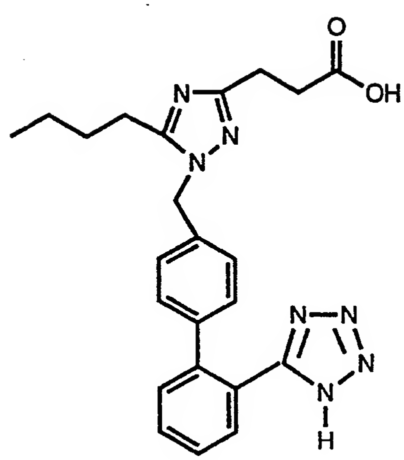
Example 62



<ins>5-[4'-[[5-butyl-3-(tricyclo[3.3.1.1$^{3.7}$]dec-1-ylmethyl]-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole</ins>

The slower moving isomer from Example 61 was deprotected to provide 5-[4'-[[5-butyl-3-(tricyclo[3.3.1.1$^{3.7}$]dec-1-ylmethyl]-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole: NMR ($CDCl_3$) δ 0.85 (t, *J* = 8 Hz, 3H), 1.21-1.37 (m, 8H), 1.44-1.58 (m, 5H), 1.62 (d, *J* = 10 Hz, 3H), 1.86 (s, 3H), 2.07 (s, 2H), 2.49 (t, *J* = 8 Hz, 2H), 5.21 (s, 2H), 6.89 (d, *J* = 8 Hz, 2H), 7.07 (d, *J* = 8 Hz, 2H), 7.53 (dd, *J* = 8 and 2 Hz, 1H), 7.52-7.65 (m, 2H), 7.91 (dd, *J* = 8 and 2 Hz, 1H), MS (FAB) m/e (rel intensity) 508 (42), 274 (22), 207 (100), 192 (34); HRMS. Calc'd for M+H: 508.3189. Found: 508.3142.

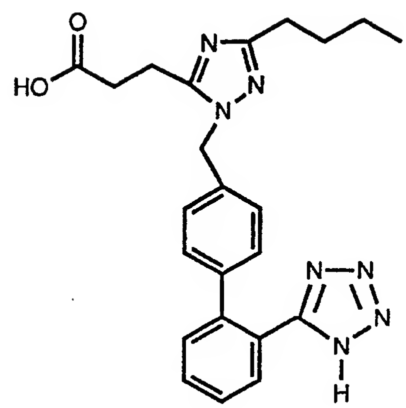
Example 63



<u>5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-3-propanoic acid</u>

A 2.18 g sample of the mixture of the two isomers from Example 45 was oxidized to the corresponding aldehydes with oxalyl chloride/dimethyl sulfoxide and subsequently oxidized to the acids with potassium permanganate to give 1.8 g of a mixture of the two propanoic isomers. Deprotection of the faster moving isomer provided 5-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-3-propanoic acid: NMR ($CDCl_3$) δ 0.99 (t, *J* = 8 Hz, 3H), 1.28-1.43 (m, 2H), 1.61-1.74 (m, 2H), 2.67-2.80 (m, 4H), 2.94 (t, *J* = 6 Hz, 2H), 5.18 (s, 2H), 7.04-7.14 (m, 4H), 7.42 (dd, *J* = 8 and 2 Hz, 1H), 7.50 (dt, *J* = 8 and 2 Hz, 1H), 7.59 (dt, *J* = 8 and 2 Hz, 1H), 7.90 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 432 (89), 389 (15), 237 (36), 198 (100); HRMS. Calc'd for M+H: 432.2148. Found: 432.2216.

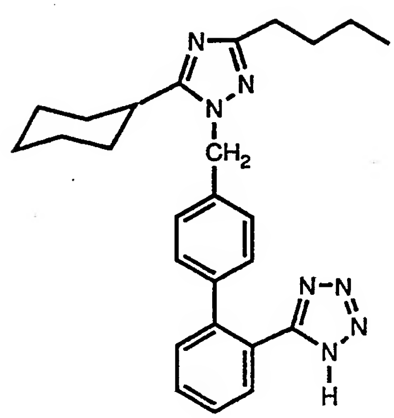
Example 64



3-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-5-propanoic acid

The slower moving isomer from Example 63 was deprotected to give 3-butyl-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazole-5-propanoic acid: NMR ($CDCl_3$) δ 0.92 (t, *J* = 8 Hz, 3H), 1.30-1.40 (m, 2H), 1.65-1.78 (m, 2H), 2.70 (t, *J* = 8 Hz, 2H), 2.84-2.91 (m, 2H), 2.93-3.00 (m, 2H), 5.40 (s, 2H), 7.20 (d, *J* = 8 Hz, 2H), 7.34 (d, *J* = 8 Hz, 2H), 7.37-7.42 (m, 1H), 7.51-7.62 (m, 2H), 8.30-8.36 (m, 1H); MS (FAB) m/e (rel intensity) 432 (100) 198 (45); HRMS. Calc'd for M+H: 432.2148. Found: 432.2214.

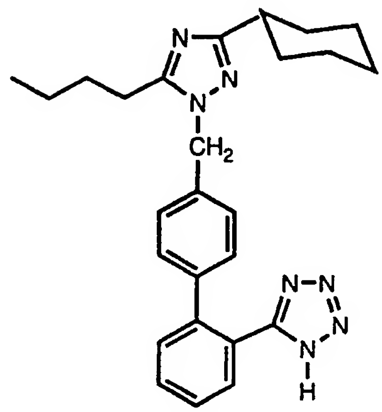
Example 65



5-[4'-[(3-butyl-5-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following General Procedure A, 2.07 g (10 mmol) of 3-butyl-5-cyclohexyl-1H-1,2,4-triazole was reacted with 6.5 g (11.8 mmol) of the alkylating reagent prepared in step 1 of Example 3 to give 6.3 g (9.2 mmol) of a mixture of the two isomers. Deprotection of the faster moving isomer provided 33 mg of 5-[4'-[(3-butyl-5-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-1,2,4-triazole as a colorless solid: mp 157.5-159.5 °C; NMR ($CDCl_3$) δ 0.87 (t, *J* = 7 Hz, 3H), 1.11-1.36 (m, 6H), 1.45-1.70 (m, 6H), 1.70-1.80 (m, 2H), 2.50 (t, *J* = 7 Hz, 2H), 2.64-2.78 (m, 1H), 5.23 (s, 2H), 6.98 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H), 7.41 (dd, *J* = 5 and 1 Hz, 1H), 7.49 (dt, *J* = 5 and 1 Hz, 1H), 7.57 (dt, *J* = 5 and 1 Hz, 1H), 7.80 (dd, *J* = 5 and 1 Hz, 1H): MS (FAB) m/e (rel intensity), 442 (100), 414 (10), 399 (20), 235 (8), 207 (65), 192 (18).

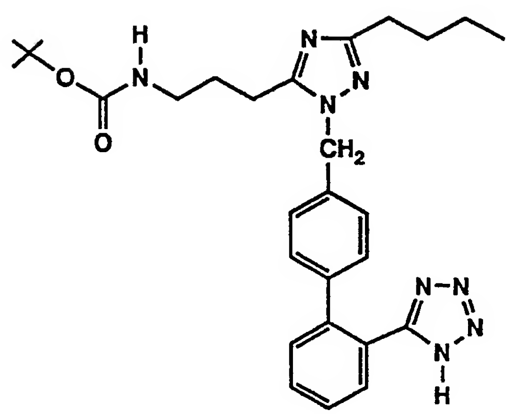
Example 66



5-[4'-[(5-butyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

The slower moving isomer from Example 65 was deprotected to provide 135 mg of 5-[4'-[(5-butyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: mp 125-127 °C; NMR ($CDCl_3$) δ 0.85 (t, *J* = 7 Hz, 3H), 1.12-1.40 (m, *J* = 8 Hz, 8H), 1.52-1.75 (m, *J* = 8 Hz, 4H), 1.81 (d, *J* = 8 Hz, 2H), 2.50 (t, *J* = 8 Hz, 3H), 5.20 (s, 2H), 6.94 (d, *J* = 8 Hz, 2H), 7.09 (d, *J* = 8 Hz, 2H), 7.42 (dd, *J* = 8 and 2 Hz, 1H), 7.50-7.64 (m, *J* = 8 Hz, 2H), 7.88 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 442 (100), 414 (10), 399 (20), 235 (10), 207 (75), 192 (17).

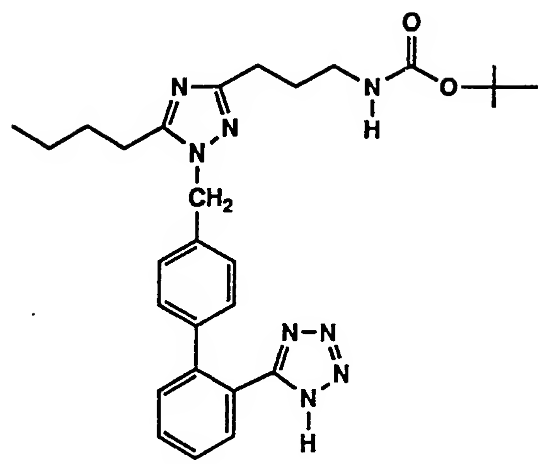
Example 67



1,1-dimethylethyl 3-butyl-[1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-5-yl]propylcarbamate

Following General Procedure A, 6.0 g (20 mmol) of 3-butyl-5-(N-Boc-3-aminopropyl)-1H-1,2,4-triazole was reacted with 13.1 g (24 mmol) of the alkylating reagent prepared in step 1 of Example 3. Deprotection of the faster moving isomer gave 3.52 g (33%) of 1,1-dimethylethyl 3-butyl-[1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-5-yl]propylcarbamate as a colorless solid: NMR (DMSO-d_6) δ 0.88 (t, *J* = 8 Hz, 3H), 1.22-1.34 (m, *J* = 8 Hz, 2H), 1.36 (s, 9H), 1.54-1.66 (m, *J* = 7 Hz, 2H), 1.66-1.78 (m, *J* = 7 Hz, 2H), 2.5 (t, *J* = 8 Hz, 2H), 2.67 (t, *J* = 8 Hz, 2H), 2.96 (q, *J* = 8 Hz, 2H), 5.26 (s, 2H), 7.08 (s, 4H), 7.55 (q, *J* = 8 Hz, 2H), 7.65 (d, *J* = 8 Hz, 2H); MS (FAB) m/e (rel intensity) 517 (60), 489 (10), 461 (10), 439 (10), 417 (23), 389 (18), 357 (8), 323 (8), 305 (15), 283 (80), 227 (70), 207 (100), 183 (65); HRMS. Calc'd for M+H: 517.3039. Found 517.3001.

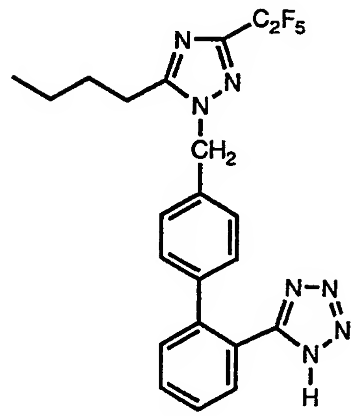
Example 68



1,1-dimethylethyl 5-butyl-[1-[2'-(1H-tetrazol-5yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-3-yl]propylcarbamate

The slower moving isomer from Example 67 was deprotected to give 3.43 g (33%) of 1,1-dimethylethyl 5-butyl-[1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-ylmethyl]-1H-1,2,4-triazol-3-yl]propylcarbamate as a colorless solid: NMR (DMSO-d_6) δ 0.84 (t, *J* = 7 Hz, 3H), 1.29 (q, *J* = 8 Hz, 2H), 1.38 (s, 9H), 1.48-1.59 (m, *J* = 8 Hz, 2H), 1.72 (t, *J* = 8 Hz, 2H), 2.53 (t, *J* = 7 Hz, 2H), 2.67 (t, *J* = 8 Hz, 2H), 2.97 (q, *J* = 8 Hz, 2H), 5.28 (s, 2H), 7.08 (s, 4H), 7.50 (d, *J* = 8 Hz, 1H) 7.55 (d, *J* = 8 Hz, 1H), 7.61-7.68 (m, *J* = 7 Hz, 2H); MS (FAB) m/e (rel intensity) 517 (40), 439 (10) 417 (40), 390 (20), 357 (10), 207 (100), 192 (40); HRMS. Calc'd for M+H: 517.3039. Found: 517.3014.

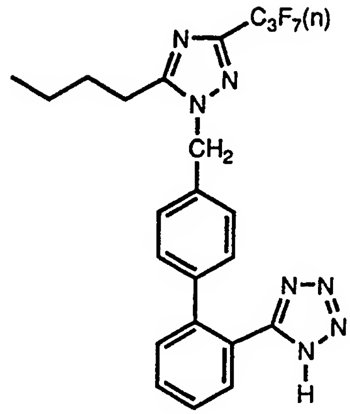
Example 69



5-[4'-[[3-(1,1,2,2,2,-pentafluoroethyl)-5-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazol

Following General Procedure A, 1.21 g (5.0 mmol) of 3-perfluoroethyl-5-butyl-1H-1,2,4-triazole was reacted with 3.2 g (5.7 mmol) of the alkylating reagent prepared in step 1 of Example 3. Deprotection provided 409 mg of 5-[4'-[[3-(1,1,2,2,2-pentafluoroethyl)-5-butyl-1H-1,2,4-triazol-1-yl]methyl[1,1-biphenyl]-2-yl]-1H-tetrazole as a colorless oil: NMR ($CDCl_3$) δ 0.90 (t, *J* = 7 Hz, 3H), 1.36 (q, *J* = 7 Hz, 2H), 1.67 (t, *J* = 7 Hz, 2H), 2.78 (t, *J* = 7 Hz, 2H), 5.38 (s, 2H), 7.18 (s, 4H), 7.42 (d, *J* = 8 Hz, 1H), 7.51-7.67 (m, *J* = 8 Hz, 2H), 7.98 (d, *J* = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 478 (40), 452 (15), 235 (90), 207 (100), 178 (40), 152 (35); HRMS. Calc'd. for M+H: 478.1778. Found: 478.1807.

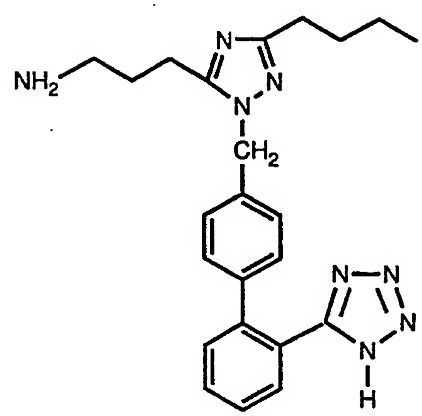
Example 70



5-[4'-[[3-(1,1,2,2,3,3,3-heptafluoropropyl)-5-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following General Procedure A, 1.46 g (5.0 mmol) of 5-butyl-3-perfluoropropyl-1H-1,2,4-triazole was reacted with 3.20 g (5.7 mmol) of the alkylating reagent prepared in step 1 of Example 3. Deprotection provided 210 mg of 5-[4'-[[3-(1,1,2,2,3,3,3-heptafluoropropyl)-5-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless oil: NMR ($CDCl_3$) δ 0.90 (t, *J* = 7 Hz, 3H), 1.36 (q, *J* = 8 Hz, 2H), 1.63-1.75 (m, *J* = 8 Hz, 2H), 2.78 (t, *J* = 8 Hz, 2H), 5.40 (s, 2H), 7.20 (q, *J* = 7 Hz, 4H), 7.42 (dd, *J* = 8 and 2 Hz, 1H), 7.52-7.65 (m, *J* = 8 Hz, 2H), 8.04 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 528 (35), 502 (15), 294 (12), 235 (90), 207 (100), 136 (15); HRMS. Calc'd for M+H: 528.1747. Found: 528.1701.

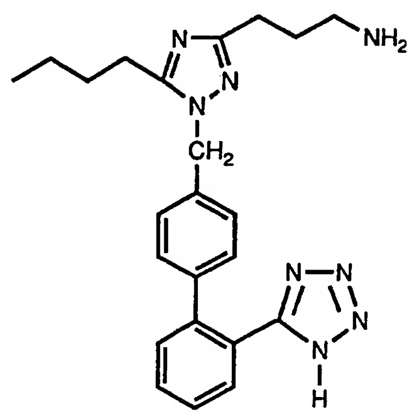
Example 71



5-[4'-[[3-butyl-5-(3-aminopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Under a static nitrogen atmosphere 2.40 g (4.7 mmol) of 5-[4'-[[3-butyl-5-(N-Boc-3-aminopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole from Example 67 was dissolved in 30 mL of 4N HCl in dioxane at ambient temperature and allowed to stir overnight. The solvents were removed *in vacuo*; the residue was triturated with diethyl ether and filtered providing 2.08 g (98%) of 5-[4'-[[3-butyl-5-(3-aminopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as the hydrochloride salt: NMR (DMSO-d_6) δ 0.88 (t, *J* = 7 Hz, 3H), 1.25-1.39 (m, 2H), 1.57-1.69 (m, 2H), 1.92-2.40 (m, 2H), 2.62 (t, *J* = 7 Hz, 2H), 2.89 (q, *J* = 8 Hz, 2H), 2.98 (t, *J* = 8 Hz, 2H), 5.38 (s, 2H), 7.10 (d, *J* = 8 Hz, 2H), 7.19 (d, *J* = 8 Hz, 2H), 7.54 (d, *J* = 8 Hz, 1H), 7.59 (dd, *J* = 8 and 2 Hz, 1H), 7.66 (s, 1H), 7.70 (dd, *J* = 8 and 2 Hz, 1H), 8.10 (br s, 2H); MS (FAB) m/e (rel intensity) 417 (38), 389 (10), 357 (10), 207 (100), 166 (50), 139 (10) 115 (10); HRMS. Calc'd for M+H: 417.2515. Found: 417.2563.

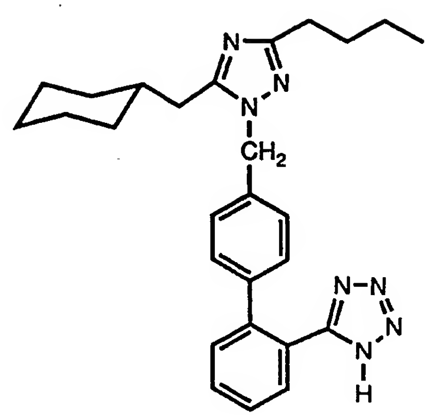
Example 72



5-[4'-[[3-(3-aminopropyl)-5-butyl-1H-1,2,4-triazol-1-yl]methyl](1,1'-biphenyl)-2-yl]-1H-tetrazole

Under a static nitrogen atmosphere 2.30 g (4.5 mmol) of 5-[4'-[[3-(N-Boc-3-aminopropyl)-5-butyl-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole from Example 68 was dissolved in 30 mL of 4N HCl in dioxane at ambient temperature and allowed to stir overnight. The solvents were removed *in vacuo*; the residue was triturated with diethyl ether and filtered providing 1.99 g (98%) of 5-[4'-[[3-(3-aminopropyl)-5-butyl-1H-1,2,4-triazol-1-yl]methyl](1,1'-biphenyl)-2-yl]-1H-tetrazole as the hydrochloride salt: NMR (DMSO-d_6) δ 0.85 (t, *J* = 7 Hz, 3H), 1.22-1.38 (m, 2H), 1.59 (t, *J* = 8 Hz, 2H), 1.96 (t, *J* = 8 Hz, 2H), 2.71-2.79 (m, 2H) 2.80-2.92 (m, 4H), 5.40 (s, 2H) 7.10 (d, *J* = 8 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H) 7.52 (d, *J* = 8 Hz, 1H), 7.59 (d, *J* = 8 Hz, 1H), 7.68 (d, *J* = 8 Hz, 2H); MS (FAB) m/e (rel intensity) 417 (60), 389 (10), 357 (10), 263 (5), 235 (10), 207 (100), 166 (40), 136 (15); HRMS. Calc'd for M+H: 417.2515. Found: 417.2510.

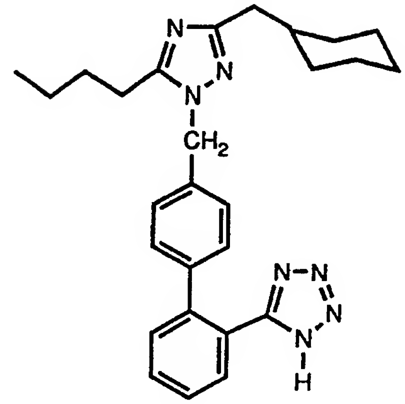
Example 73



5-[4'-[(3-butyl-5-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Following General Procedure A, 2.21 g (10.0 mmol) of 3-butyl-5-cyclohexylmethyl-1H-1,2,4-triazole was reacted with 6.55 g (11.8 mmol) of the alkylating reagent prepared in step 1 of Example 3 to give 5.90 g (85%) of a mixture of the two isomers. The faster moving isomer was deprotected to provide 64 mg of 5-[4'-[(3-butyl-5-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: NMR ($CDCl_3$) δ 0.92 (t, J = 7 Hz, 3H) 0.94-1.05 (m, 2H) 1.08-1.25 (m, 3H), 1.25-1.41 (m, 2H), 1.55-1.80 (m, 8H), 2.65 (d, J = 7 Hz, 2H), 2.68 (t, J = 7 Hz, 2H), 5.27 (s, 2H), 7.11 (q, J = 8 Hz, 4H), 7.42 (dd, J = 8 and 2 Hz, 1H), 7.49-7.63 (m, 2H), 7.94 (dd, J = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 456 (100), 428 (10), 413 (20), 280 (10), 235 (10), 222 (25), 207 (80), 192 (30); HRMS. Calc'd for M+H: 456.2876. Found: 456.2839.

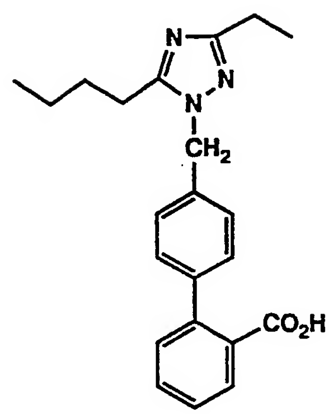
Example 74



5-[4'-[(3-cyclohexylmethyl-5-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

The slower moving isomer from Example 73 was deprotected to provide 51 mg of 5-[4'-[(3-cyclohexylmethyl-5-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole as a colorless solid: NMR ($CDCl_3$) δ 0.84 (t, *J* = 8 Hz, 3H), 0.92 (q, *J* = 8 Hz, 2H), 1.05-1.22 (m, 3H), 1.22-1.36 (m, 2H), 1.52-1.69 (m, 8H), 2.50 (d, *J* = 7 Hz, 2H), 2.63 (t, *J* = 8 Hz, 2H), 5.18 (s, 2H), 7.05 (q, *J* = 8 Hz, 4H), 7.35-7.55 (m, 3H), 7.68 (dd, *J* = 8 and 2 Hz, 1H); MS (FAB) m/e (rel intensity) 456 (90), 413 (10), 281 (10), 243 (10), 222 (35), 207 (100), 192 (35); HRMS. Calc'd for M+H: 456.2876. Found: 456.2849.

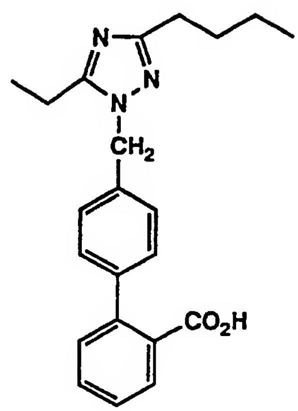
Example 75



4'-[(3-ethyl-5-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid

Following General Procedure A, 1.0 g (6.0 mmol) of 3-ethyl-5-butyl-1H-1,2,4-triazole was reacted with 2.41 g (7.9 mmol) of the alkylating reagent prepared in step 1 of Example 1. Hydrolysis of the faster moving isomer provided 220 mg of 4'-[(3-ethyl-5-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid as a colorless solid: NMR (DMSO-d_6) δ 0.85 (t, *J* = 7 Hz, 3H), 1.19 (t, *J* = 7 Hz, 3H), 1.27-1.38 (m, 2H), 1.52-1.63 (m, 2H), 2.59 (q, *J* = 7 Hz, 2H), 2.74 (t, *J* = 7 Hz, 2H), 5.35 (s, 2H), 7.21 (d, *J* = 8 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H), 7.35 (dd, *J* = 8 and 2 Hz, 1H), 7.48 (dt, *J* = 8 and 2 Hz, 1H), 7.57 (dt, *J* = 8 and 2 Hz, 1H), 7.72 (dd, *J* = 8 and 2 Hz, 1H).

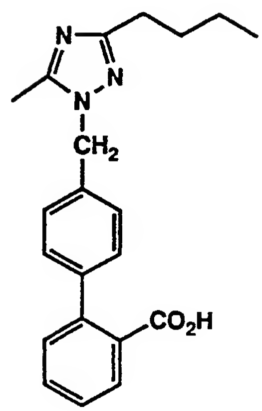
Example 76



4'-[(3-butyl-5-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid

The slower moving isomer from Example 75 was hydrolyzed to provide 174 mg of 4'-[(3-butyl-5-ethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid as a colorless solid: NMR (DMSO-d_6) δ 0.89 (t, *J* = 7 Hz, 3H), 1.17 (t, *J* = 7 Hz, 3H), 1.27-1.40 (m, 2H), 1.56-1.68 (m, 2H), 2.58 (t, *J* = 8 Hz, 2H), 2.77 (q, *J* = 8 Hz, 2H), 5.35 s, 2H), 7.21 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 7.36 (dd, *J* = 8 and 2 Hz, 1H), 7.46 (dt, *J* = 8 and 2 Hz, 1H), 7.57 (dt, *J* = 8 and 2 Hz, 1H), 7.73 (dd, *J* = 8 and 2 Hz, 1H).

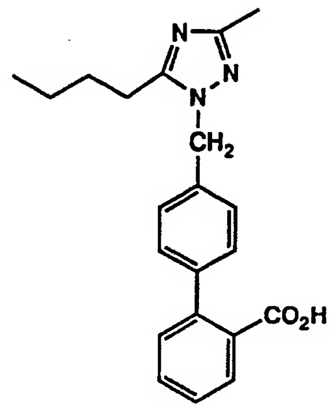
Example 77



4'-[(3-butyl-5-methyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid

Following General Procedure A, 1.0 g (7.2 mmol) of 3-butyl-5-methyl-1H-1,2,4-triazole was reacted with 2.89 g (9.5 mmol) of the alkylating reagent prepared in step 1 of Example 1. Hydrolysis of the slower moving isomer provided 220 mg of 4'-[(3-butyl-5-methyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid as a colorless solid: NMR (DMSO-d_6) δ 0.88 (t, *J* = 7 Hz, 3H), 1.25-1.38 (m, 2H), 1.54-1.67 (m, 2H), 2.39 (s, 3H), 2.54 (t, *J* = 8 Hz, 2H), 5.32 (s, 2H), 7.21 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 7.36 (dd, *J* = 8 and 2 Hz, 1H), 7.46 (dt, *J* = 8 and 2 Hz, 1H), 7.56 (dt, *J* = 8 and 2 Hz, 1H), 7.72 (dd, *J* = 8 and 2 Hz, 1H).

Example 78



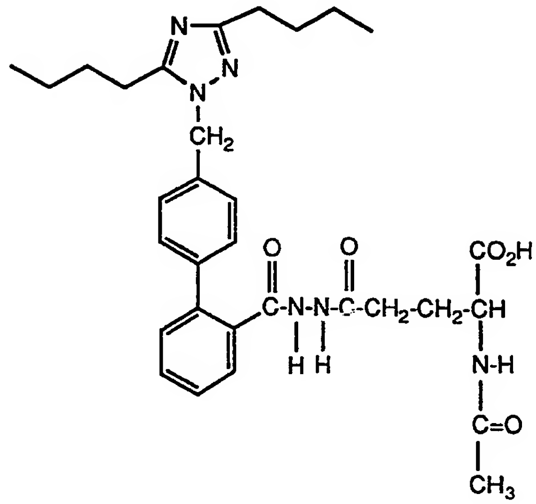
4'-[(3-methyl-5-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid

The faster moving isomer from Example 77 was hydrolyzed to provide 19 mg of 4'-[(3-methyl-5-butyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid as a colorless solid: NMR (DMSO-d_6) δ 0.86 (t, *J* = 7 Hz, 3H), 1.25-1.38 (m, 2H), 1.52-1.64 (m, 2H), 2.21 (s, 3H), 2.72 (t, *J* = 7 Hz, 2H), 5.32 (s, 2H), 7.21 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 7.35 (dd, *J* = 8 and 2 Hz, 1H), 7.45 (dt, *J* = 8 and 2 Hz, 1H), 7.57 (dt, *J* = 8 and 2 Hz, 1H), 7.72 (dd, *J* = 8 and 2 Hz, 1H).

A class of highly preferred specific conjugates of the invention is provided by conjugates formed from a biphenylmethyl 1H-substituted-1,2,4-triazole AII antagonist compound linked to a cleavable glutamyl residue. Each conjugate of this class contains a diamino linker moiety which connects a terminal carboxylic acid moiety on the biphenylmethyl portion of the AII antagonist compound with a terminal carboxylic acid moiety on the gamma carbon of the cleavable glutamyl residue. Example #79 is a detailed description of a conjugate of this class. Other specific conjugates of Examples #80-#144, as shown in Table IV, may

be prepared generally in accordance with the procedures of Example #79.

Example 79



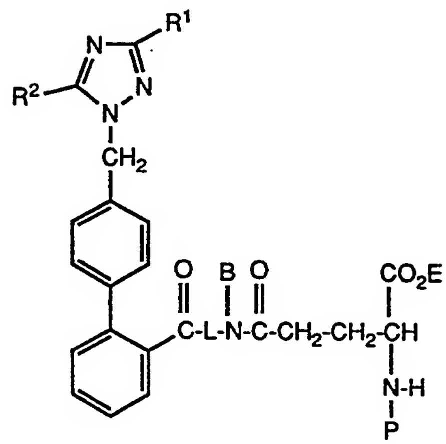
N-acetylglutamic acid, 5-[[4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]]carbonylhydrazide

To a solution of 10.45 g (34.5 mmol) of N-Boc-L-glutamic acid-α-tertbutyl ester (BACHEM) in 100 mL of methylene chloride under nitrogen was added 3.5 g (17.0 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction was allowed to stir for 2 h and filtered under nitrogen. The anhydride solution was then added to a solution of 6.03 g (14.9 mmol) of the compound of Example 4 in 75 mL of methylene chloride under nitrogen. The reaction was stirred overnight and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500A) using ethyl acetate gave 7.90 g (77%) of pure material by thin-layer chromatography (TLC). This material was redissolved in 100 mL of methylene chloride under nitrogen and cooled to 0°C prior to the addition of 135 mL

of TFA. The stirred reaction was allowed to warm to ambient temperature overnight and concentrated in vacuo.

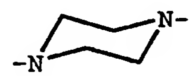
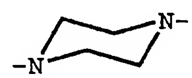
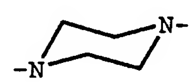
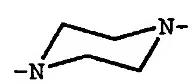
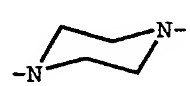
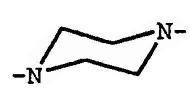
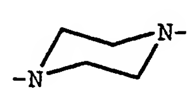
The crude product was dissolved in 80 mL of acetonitrile/water (1:1) and the pH adjusted to 9 with 1 M K_2CO_3. The solution was cooled to 0°C and 1.1 mL (11 mmol) of acetic anhydride and 11 mL (11 mmol) of 1 M K_2CO_3 was added every 30 min for 5 h; during the course of this reaction the pH was maintained at 9 and the reaction temperature kept below 5°C. After the last addition, the reaction was allowed to warm to ambient temperature overnight. The pH was adjusted to 4 with 3 M HCl and the reaction concentrated to 300 mL. Purification by reverse phase chromatography (Waters Delta prep-3000) using isocratic 32% acetonitrile/water (0.05% TFA) gave 6.11 g (55%-overall yield from the compound of Example 4) of colorless product: NMR (DMSO-d_6) δ 0.85 (t, *J* = 8Hz, 3H), 0.88 (t, *J* = 8Hz, 3H), 1.23-1.39 (m, 4H), 1.53-1.68 (m, 6H), 1.84 (s, 3H), 2.15-2.24 (m, 2H), 2.55 (t, *J* = 8Hz, 2H), 2.70 (t, *J* = 8Hz, 2H), 4.10-4.20 (m, 1H), 5.31 (s, 2H), 7.11-7.19 (m, 2H), 7.37-7.57 (m, 6H); MS (FAB) m/e (rel intensity) 577 (42), 389 (10), 195 (82), 182 (100), 167 (63), 152 (28); HRMS. Calcd . for M+H: 577.3138. Found: 577.3160. Anal. Calcd. for $C_{31}H_{40}N_6O_5 \cdot 1.5\ CF_3CO_2H$: C, 54.65; H, 5.56; N, 11.25; F, 11.50. Found: C, 54.42; H, 5.75, N, 11.35, F, 11.85.

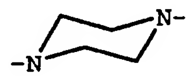
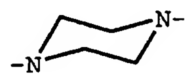
TABLE IV



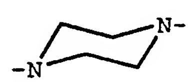
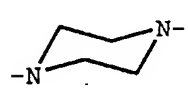
Ex. #	R^1	R^2	L	B	E	P
80	C_4H_9 (n)	C_4H_9 (n)	-NH-	H	H	H
81	C_4H_9 (n)	C_4H_9 (n)	-NH-	H	CH_3	H
82	C_4H_9 (n)	C_4H_9 (n)	-NH-	H	CH_3	$COCH_3$
83	C_4H_9 (n)	C_4H_9 (n)	-NH-	H	C_2H_5	$COCH_3$
84	C_4H_9 (n)	C_4H_9 (n)	-NH-	H	C_2H_5	H
85	C_4H_9 (n)	C_4H_9 (n)	-NH-	H	H	$COCH_2Cl$
86	C_4H_9 (n)	C_4H_9 (n)	-NH-	H	H	COC_4H_9 (n)
87	Cl	C_4H_9 (n)	-NH-	H	H	$COCH_3$

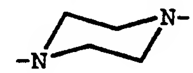
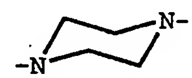
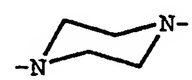
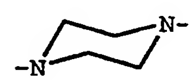
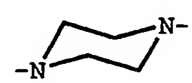
Ex. #	R^1	R^2	L	B	E	P
88	Cl	C_4H_9(n)	-NH-	H	H	H
89	C_4H_9(n)	C_4H_9(n)	$-NHCH_2CH_2-$	H	H	$COCH_3$
90	C_4H_9(n)	C_4H_9(n)	$-NHCH_2CH_2-$	H	H	H
91	C_4H_9(n)	C_4H_9(n)	$-NHCH_2CH_2-$	H	CH_3	H
92	C_4H_9(n)	C_4H_9(n)	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
93	C_4H_9(n)	C_4H_9(n)	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
94	C_4H_9(n)	C_4H_9(n)	$-NHCH_2CH_2-$	H	C_2H_5	H
95	C_4H_9(n)	C_4H_9(n)	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
96	C_4H_9(n)	C_4H_9(n)	$-NHCH_2CH_2-$	H	H	COC_4H_9(n)
97	Cl	C_4H_9(n)	$-NHCH_2CH_2-$	H	H	$COCH_3$
98	Cl	C_4H_9(n)	$-NHCH_2CH_2-$	H	H	H

Ex. #	R^1	R^2	L	B	E	P
99	C_4H_9 (n)	C_4H_9 (n)		*	H	$COCH_3$
100	C_4H_9 (n)	C_4H_9 (n)		*	H	H
101	C_4H_9 (n)	C_4H_9 (n)		*	CH_3	H
102	C_4H_9 (n)	C_4H_9 (n)		*	CH_3	$COCH_3$
103	C_4H_9 (n)	C_4H_9 (n)		*	C_2H_5	$COCH_3$
104	C_4H_9 (n)	C_4H_9 (n)		*	C_2H_5	H
105	C_4H_9 (n)	C_4H_9 (n)		*	H	COC_4H_9 (n))
106	C_4H_9 (n)	C_4H_9 (n)		H	H	COC_4H_9 (n))

Ex. #	R^1	R^2	L	B	E	P
107	Cl	C_4H_9 (n)		*	H	$COCH_3$
108	Cl	C_4H_9 (n)		*	H	H .
109	C_2H_5	C_4H_9 (n)	-NH-	H	H	$COCH_3$
110	C_2H_5	C_4H_9 (n)	-NH-	H	H	H
111	C_3H_7 (n)	C_4H_9 (n)	-NH-	H	H	$COCH_3$
112	C_3H_7 (n)	C_4H_9 (n)	-NH-	H	H	H
113	C_5H_{11} (n)	C_4H_9 (n)	-NH-	H	H	$COCH_3$
114	C_5H_{11} (n)	C_4H_9 (n)	-NH-	H	H	H
115	C_6H_{13} (n)	C_4H_9 (n)	-NH-	H	H	$COCH_3$
116	C_6H_{13} (n)	C_4H_9 (n)	-NH-	H	H	H
117	$CF_2CH_2CH_2CH_3$	C_4H_9 (n)	-NH-	H	H	$COCH_3$

Ex. #	R^1	R^2	L	B	E	P
118	$CF_2CH_2CH_2CH_3$	C_4H_9(n)	-NH-	H	H	H
119	$CH_2CH_2CH(CH_3)_2$	C_4H_9(n)	-NH-	H	H	$COCH_3$
120	$CH_2CH_2CH(CH_3)_2$	C_4H_9(n)	-NH-	H	H	H
121	C_2H_5	C_2H_5	-NH-	H	H	$COCH_3$
122	C_2H_5	C_2H_5	-NH-	H	H	H
123	C_3H_7(n)	C_3H_7(n)	-NH-	H	H	$COCH_3$
124	C_3H_7(n)	C_3H_7(n)	-NH-	H	H	$COCH_3$
125	C_5H_{11}(n)	C_5H_{11}(n)	-NH-	H	H	$COCH_3$
126	C_5H_{11}(n)	C_5H_{11}(n)	-NH-	H	H	H
127	C_6H_{13}(n)	C_6H_{13}(n)	-NH-	H	H	$COCH_3$
128	C_6H_{13}(n)	C_6H_{13}(n)	-NH-	H	H	H

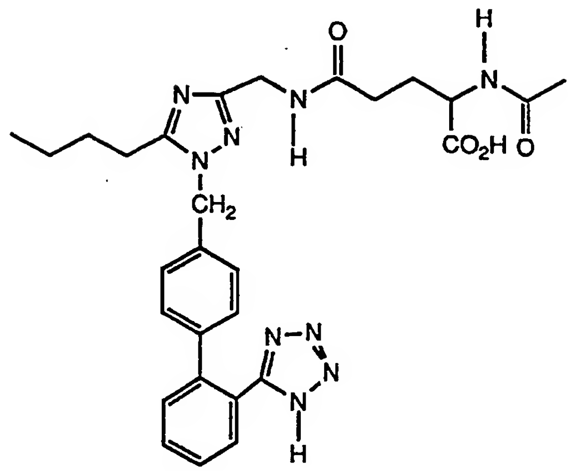
Ex. #	R^1	R^2	L	B	E	P
129	C_2H_5	C_2H_5	$-NHCH_2CH_2-$	H	H	$COCH_3$
130	C_2H_5	C_2H_5	$-NHCH_2CH_2-$	H	H	H
131	C_3H_7 (n)	C_3H_7 (n)	$-NHCH_2CH_2-$	H	H	$COCH_3$
132	C_3H_7 (n)	C_3H_7 (n)	$-NHCH_2CH_2-$	H	H	H
133	C_5H_{11} (n)	C_5H_{11} (n)	$-NHCH_2CH_2-$	H	H	$COCH_3$
134	C_5H_{11} (n)	C_5H_{11} (n)	$-NHCH_2CH_2-$	H	H	H
135	C_6H_{13} (n)	C_6H_{13} (n)	$-NHCH_2CH_2-$	H	H	$COCH_3$
136	C_6H_{13} (n)	C_6H_{13} (n)	$-NHCH_2CH_2-$	H	H	H
137	C_2H_5	C_2H_5		*	H	$COCH_3$
138	C_2H_5	C_2H_5		*	H	H

Ex. #	R^1	R^2	L	B	E	P
139	C_3H_7 (n)	C_3H_7 (n)		*	H	$COCH_3$
140	C_3H_7 (n)	C_3H_7 (n)		*	H	H
141	C_5H_{11} (n) C_5H_{11} (n)	C_5H_{11} (n)		*	H	$COCH_3$81
142	C_5H_{11} (n)	C_5H_{11} (n)		*	H	H
143	C_6H_{13} (n)	C_6H_{13} (n)		*	H	$COCH_3$
144	C_6H_{13} (n)	C_6H_{13} (n)		*	H	H

* B IS INCORPORATED IN A

Another preferred class of specific conjugates of the invention is provided by conjugates formed from a biphenylmethyl 1H-substituted-1,2,4-triazole AII antagonist compound linked to a cleavable glutamyl residue. Each conjugate of this class contains a terminal amino moiety on the triazole portion of the AII antagonist compound which is connected to a terminal carboxylic acid moiety on the gamma carbon of the cleavable glutamyl residue. Example #145 is a detailed description of a conjugate of this class. Other specific conjugates of Examples #146-#426, as shown in Table V, may be prepared generally in accordance with the procedures of Example #145.

Example 145

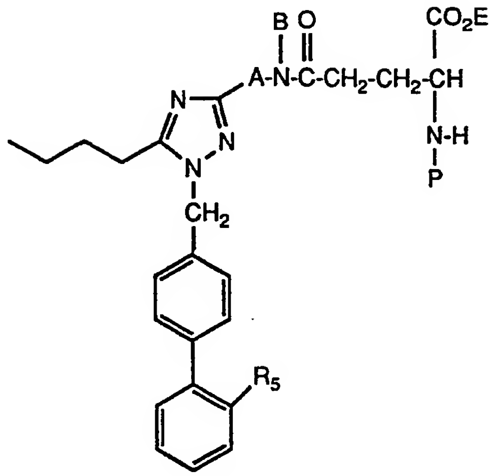


N^2-acetyl-N-[[5-butyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1,2,4-triazol-3-yl]methyl]-L-glutamine

To a solution of 10.45 g (34.5 mmol) of N-Boc-L-glutamic acid-α-tertbutyl ester (BACHEM) in 100 mL of methylene chloride under nitrogen is added 3.5 g (17.0 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and filtered under nitrogen. The anhydride solution is then added to a solution of 5.78 g (14.9 mmol) of the compound of Example 3 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight and concentrated _in vacuo_. Purification by silica gel chromatography (Waters Prep-500A) gives pure material by thin-layer chromatography (TLC). This material is redissolved in 100 mL of methylene chloride under nitrogen and is cooled to 0°C prior to the addition of 135 mL of TFA. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated _in vacuo_. The crude product is dissolved in 80 mL of acetonitrile/water (1:1) and the pH is adjusted to 9 with 1 M K_2CO_3. The solution is cooled to 0°C and 1.1 mL (11 mmol) of acetic anhydride and 11 mL (11 mmol) of 1 M K_2CO_3 is added every 30 min for 5 h; during the course of

this reaction the pH is maintained at 9 and the reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 300 mL. Purification by reverse phase chromatography (Waters Delta prep-3000) gives N^2-acetyl-N-[[5-butyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1,2,4-triazol-3-yl]methyl]-L-glutamine.

TABLE V



Ex: #	R_5	A	B	E	P
146	CO_2H	single bond	H	H	$COCH_3$
147	CO_2H	single bond	H	H	$COCH_2Cl$
148	CO_2H	single bond	H	H	COC_4H_9
149	CO_2H	single bond	H	CH_3	$COCH_3$
150	CO_2H	single bond	H	C_2H_5	$COCH_3$
151	CN_4H	single bond	H	H	$COCH_3$
152	CN_4H	single bond	H	H	$COCH_2Cl$
153	CN_4H	single bond	H	H	COC_4H_9

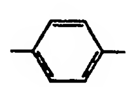
Ex: #	R_5	A	B	E	P
154	CN_4H	single bond	H	CH_3	$COCH_3$
155	CN_4H	single bond	H	C_2H_5	$COCH_3$
156	CO_2H	single bond	H	H	H
157	CO_2H	single bond	H	CH_3	H
158	CO_2H	single bond	H	C_2H_5	H
159	CN_4H	single bond	H	H	H
160	CN_4H	single bond	H	CH_3	H
161	CN_4H	single bond	H	C_2H_5	H
162	CO_2H	$-CH_2-$	H	H	$COCH_3$
163	CO_2H	single bond	H	H	$COCH_2Cl$
164	CO_2H	single bond	H	H	COC_4H_9
165	CO_2H	single bond	H	CH_3	$COCH_3$
166	CO_2H	single bond	H	C_2H_5	$COCH_3$

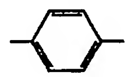
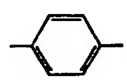
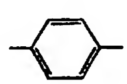
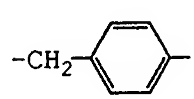
Ex: #	R_5	A	B	E	P
167	CN_4H	single bond	H	H	$COCH_2Cl$
168	CN_4H	single bond	H	H	COC_4H_9
169	CN_4H	single bond	H	CH_3	$COCH_3$
170	CN_4H	single bond	H	C_2H_5	$COCH_3$
171	CO_2H	$-CH_2-$	H	H	H
172	CO_2H	single bond	H	CH_3	H
173	CO_2H	single bond	H	C_2H_5	H
174	CN_4H	$-CH_2-$	H	H	H
175	CN_4H	single bond	H	CH_3	H
176	CN_4H	single bond	H	C_2H_5	H
177	CN_4H	$-CH_2-$	CH_3	H	H
178	CN_4H	$-CH_2-$	CH_3	H	$COCH_3$
179	CO_2H	$-CH_2CH_2-$	H	H	$COCH_3$

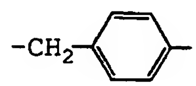
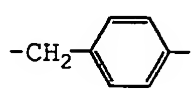
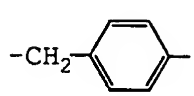
Ex: #	R_5	A	B	E	P
180	CO_2H	single bond	H	H	$COCH_2Cl$
181	CO_2H	single bond	H	H	COC_4H_9
182	CO_2H	single bond	H	CH_3	$COCH_3$
183	CO_2H	single bond	H	C_2H_5	$COCH_3$
184	CN_4H	$-CH_2CH_2-$	H	H	$COCH_3$
185	CN_4H	single bond	H	H	$COCH_2Cl$
186	CN_4H	single bond	H	H	COC_4H_9
187	CN_4H	single bond	H	CH_3	$COCH_3$
188	CN_4H	single bond	H	C_2H_5	$COCH_3$
189	CO_2H	$-CH_2CH_2-$	H	H	H
190	CO_2H	single bond	H	CH_3	H
191	CO_2H	single bond	H	C_2H_5	H
192	CN_4H	$-CH_2CH_2-$	H	H	H

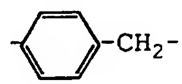
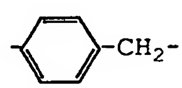
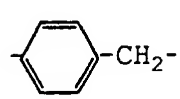
Ex: #	R_5	A	B	E	P
193	CN_4H	single bond	H	CH_3	H
194	CN_4H	single bond	H	C_2H_5	H
195	CO_2H	C_3H_6 (n)	H	H	$COCH_3$
196	CO_2H	single bond	H	H	$COCH_2Cl$
197	CO_2H	single bond	H	H	COC_4H_9
198	CO_2H	single bond	H	CH_3	$COCH_3$
199	CO_2H	single bond	H	C_2H_5	$COCH_3$
200	CN_4H	C_3H_6 (n)	H	H	$COCH_3$
201	CN_4H	single bond	H	H	$COCH_2Cl$
202	CN_4H	single bond	H	H	COC_4H_9
203	CN_4H	single bond	H	CH_3	$COCH_3$
204	CN_4H	single bond	H	C_2H_5	$COCH_3$
205	CO_2H	C_3H_6 (n)	H	H	H

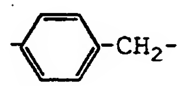
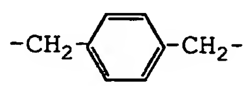
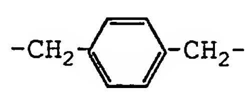
Ex: #	R_5	A	B	E	P
206	CO_2H	single bond	H	CH_3	H
207	CO_2H	single bond	H	C_2H_5	H
208	CN_4H	C_3H_6 (n)	H	H	H
209	CN_4H	single bond	H	CH_3	H
210	CN_4H	single bond	H	C_2H_5	H
211	CO_2H	C_4H_8 (n)	H	H	$COCH_3$
212	CO_2H	single bond	H	H	$COCH_2Cl$
213	CO_2H	single bond	H	H	COC_4H_9
214	CO_2H	single bond	H	CH_3	$COCH_3$
215	CO_2H	single bond	H	C_2H_5	$COCH_3$
216	CN_4H	C_4H_8 (n)	H	H	$COCH_3$
217	CN_4H	single bond	H	H	$COCH_2Cl$
218	CN_4H	single bond	H	H	COC_4H_9

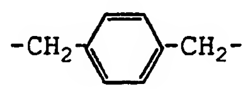
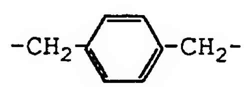
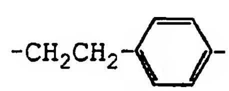
Ex: #	R_5	A	B	E	P
219	CN_4H	single bond	H	CH_3	$COCH_3$
220	CN_4H	single bond	H	C_2H_5	$COCH_3$
221	CO_2H	C_4H_8 (n)	H	H	H
222	CO_2H	single bond	H	CH_3	H
223	CO_2H	single bond	H	C_2H_5	H
224	CN_4H	C_4H_8 (n)	H	H	H
225	CN_4H	single bond	H	CH_3	H
226	CN_4H	single bond	H	C_2H_5	H
227	CO_2H		H	H	$COCH_3$
228	CO_2H	single bond	H	H	$COCH_2Cl$
229	CO_2H	single bond	H	H	COC_4H_9
230	CO_2H	single bond	H	CH_3	$COCH_3$
231	CO_2H	single bond	H	C_2H_5	$COCH_3$

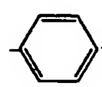
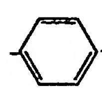
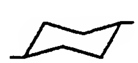
Ex: #	R_5	A	B	E	P
232	CN_4H		H	H	$COCH_3$
233	CN_4H	single bond	H	H	$COCH_2Cl$
234	CN_4H	single bond	H	H	COC_4H_9
235	CN_4H	single bond	H	CH_3	$COCH_3$
236	CN_4H	single bond	H	C_2H_5	$COCH_3$
237	CO_2H		H	H	H
238	CO_2H	single bond	H	CH_3	H
239	CO_2H	single bond	H	C_2H_5	H
240	CN_4H		H	H	H
241	CN_4H	single bond	H	CH_3	H
242	CN_4H	single bond	H	C_2H_5	H
243	CO_2H		H	H	$COCH_3$
244	CO_2H	single bond	H	H	$COCH_2Cl$

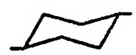
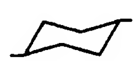
Ex: #	R_5	A	B	E	P
245	CO_2H	single bond	H	H	COC_4H_9
246	CO_2H	single bond	H	CH_3	$COCH_3$
247	CO_2H	single bond	H	C_2H_5	$COCH_3$
248	CN_4H		H	H	$COCH_3$
249	CN_4H	single bond	H	H	$COCH_2Cl$
250	CN_4H	single bond	H	H	COC_4H_9
251	CN_4H	single bond	H	CH_3	$COCH_3$
252	CN_4H	single bond	H	C_2H_5	$COCH_3$
253	CO_2H		H	H	H
254	CO_2H	single bond	H	CH_3	H
255	CO_2H	single bond	H	C_2H_5	H
256	CN_4H		H	H	H

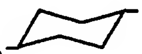
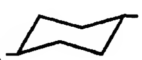
Ex: #	R_5	A	B	E	P
257	CN_4H	single bond	H	CH_3	H
258	CN_4H	single bond	H	C_2H_5	H
259	CO_2H		H	H	$COCH_3$
260	CO_2H	single bond	H	H	$COCH_2Cl$
261	CO_2H	single bond	H	H	COC_4H_9
262	CO_2H	single bond	H	CH_3	$COCH_3$
263	CO_2H	single bond	H	C_2H_5	$COCH_3$
264	CN_4H		H	H	$COCH_3$
265	CN_4H	single bond	H	H	$COCH_2Cl$
266	CN_4H	single bond	H	H	COC_4H_9
267	CN_4H	single bond	H	CH_3	$COCH_3$
268	CN_4H	single bond	H	C_2H_5	$COCH_3$
269	CO_2H		H	H	H

Ex: #	R_5	A	B	E	P
270	CO_2H	single bond	H	CH_3	H
271	CO_2H	single bond	H	C_2H_5	H
272	CN_4H		H	H	H
273	CN_4H	single bond	H	CH_3	H
274	CN_4H	single bond	H	C_2H_5	H
275	CO_2H		H	H	$COCH_3$
276	CO_2H	single bond	H	H	$COCH_2Cl$
277	CO_2H	single bond	H	H	COC_4H_9
278	CO_2H	single bond	H	CH_3	$COCH_3$
279	CO_2H	single bond	H	C_2H_5	$COCH_3$
280	CN_4H		H	H	$COCH_3$
281	CN_4H	single bond	H	H	$COCH_2Cl$
282	CN_4H	single bond	H	H	COC_4H_9

Ex: #	R_5	A	B	E	P
283	CN_4H	single bond	H	CH_3	$COCH_3$
284	CN_4H	single bond	H	C_2H_5	$COCH_3$
285	CO_2H		H	H	H
286	CO_2H	single bond	H	CH_3	H
287	CO_2H	single bond	H	C_2H_5	H
288	CN_4H		H	H	H
289	CN_4H	single bond	H	CH_3	H
290	CN_4H	single bond	H	C_2H_5	H
291	CN_4H		H	H	$COCH_3$
292	CO_2H	single bond	H	H	$COCH_2Cl$
293	CO_2H	single bond	H	H	COC_4H_9
294	CO_2H	single bond	H	CH_3	$COCH_3$
295	CO_2H	single bond	H	C_2H_5	$COCH_3$

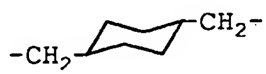
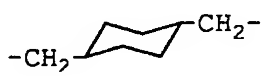
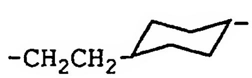
Ex: #	R_5	A	B	E	P
296	CN_4H	$-CH_2CH_2-$	H	H	H
297	CN_4H	single bond	H	H	$COCH_2Cl$
298	CN_4H	single bond	H	H	COC_4H_9
299	CN_4H	single bond	H	CH_3	$COCH_3$
300	CN_4H	single bond	H	C_2H_5	$COCH_3$
301	CN_4H	$-CH_2-CH_2-$	H	H	$COCH_3$
302	CO_2H	single bond	H	CH_3	H
303	CO_2H	single bond	H	C_2H_5	H
304	CN_4H	$-CH_2-CH_2-$	H	H	H
305	CN_4H	single bond	H	CH_3	H
306	CN_4H	single bond	H	C_2H_5	H
307	CO_2H		H	H	$COCH_3$
308	CO_2H	single bond	H	H	$COCH_2Cl$

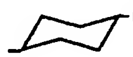
Ex: #	R_5	A	B	E	P
309	CO_2H	single bond	H	H	COC_4H_9
310	CO_2H	single bond	H	CH_3	$COCH_3$
311	CO_2H	single bond	H	C_2H_5	$COCH_3$
312	CN_4H		H	H	$COCH_3$
313	CN_4H	single bond	H	H	$COCH_2Cl$
314	CN_4H	single bond	H	H	COC_4H_9
315	CN_4H	single bond	H	CH_3	$COCH_3$
316	CN_4H	single bond	H	C_2H_5	$COCH_3$
317	CO_2H		H	H	H
318	CO_2H	single bond	H	CH_3	H
319	CO_2H	single bond	H	C_2H_5	H
320	CN_4H		H	H	H
321	CN_4H	single bond	H	CH_3	H

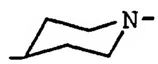
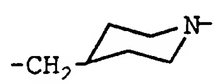
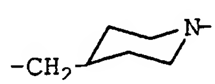
Ex: #	R_5	A	B	E	P
322	CN_4H	single bond	H	C_2H_5	H
323	CO_2H	$-CH_2-$ 	H	H	$COCH_3$
324	CO_2H	single bond	H	H	$COCH_2Cl$
325	CO_2H	single bond	H	H	COC_4H_9
326	CO_2H	single bond	H	CH_3	$COCH_3$
327	CO_2H	single bond	H	C_2H_5	$COCH_3$
328	CN_4H	$-CH_2-$ 	H	H	$COCH_3$
329	CN_4H	single bond	H	H	$COCH_2Cl$
330	CN_4H	single bond	H	H	COC_4H_9
331	CN_4H	single bond	H	CH_3	$COCH_3$
332	CN_4H	single bond	H	C_2H_5	$COCH_3$
333	CO_2H	$-CH_2-$ 	H	H	H
334	CO_2H	single bond	H	CH_3	H
335	CO_2H	single bond	H	C_2H_5	H

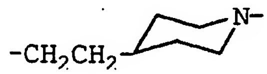
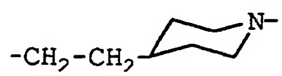
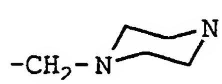
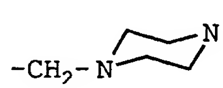
Ex: #	R_5	A	B	E	P
336	CN_4H		H	H	H
337	CN_4H	single bond	H	CH_3	H
338	CN_4H	single bond	H	C_2H_5	H
339	CO_2H		H	H	$COCH_3$
340	CO_2H	single bond	H	H	$COCH_2Cl$
341	CO_2H	single bond	H	H	COC_4H_9
342	CO_2H	single bond	H	CH_3	$COCH_3$
343	CO_2H	single bond	H	C_2H_5	$COCH_3$
344	CN_4H		H	H	$COCH_3$
345	CN_4H	single bond	H	H	$COCH_2Cl$
346	CN_4H	single bond	H	H	COC_4H_9
347	CN_4H	single bond	H	CH_3	$COCH_3$
348	CN_4H	single bond	H	C_2H_5	$COCH_3$

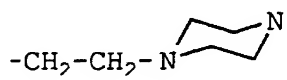
Ex: #	R_5	A	B	E	P
349	CO_2H		H	H	H
350	CO_2H	single bond	H	CH_3	H
351	CO_2H	single bond	H	C_2H_5	H
352	CN_4H		H	H	H
353	CN_4H	single bond	H	CH_3	H
354	CN_4H	single bond	H	C_2H_5	H
355	CO_2H		H	H	$COCH_3$
356	CO_2H	single bond	H	H	$COCH_2Cl$
357	CO_2H	single bond	H	H	COC_4H_9
358	CO_2H	single bond	H	CH_3	$COCH_3$
359	CO_2H	single bond	H	C_2H_5	$COCH_3$
360	CN_4H		H	H	$COCH_3$
361	CN_4H	single bond	H	H	$COCH_2Cl$
362	CN_4H	single bond	H	H	COC_4H_9

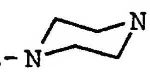
Ex: #	R_5	A	B	E	P
363	CN_4H	single bond	H	CH_3	$COCH_3$
364	CN_4H	single bond	H	C_2H_5	$COCH_3$
365	CO_2H		H	H	H
366	CO_2H	single bond	H	CH_3	H
367	CO_2H	single bond	H	C_2H_5	H
368	CN_4H		H	H	H
369	CN_4H	single bond	H	CH_3	H
370	CN_4H	single bond	H	C_2H_5	H
371	CN_4H		H	H	$COCH_3$
372	CO_2H	single bond	H	H	$COCH_2Cl$
373	CO_2H	single bond	H	H	COC_4H_9
374	CO_2H	single bond	H	CH_3	$COCH_3$
375	CO_2H	single bond	H	C_2H_5	$COCH_3$

Ex: #	R_5	A	B	E	P
376	CN_4H	$-CH_2CH_2-$	H	H	H
377	CN_4H	single bond	H	H	$COCH_2Cl$
378	CN_4H	single bond	H	H	COC_4H_9
379	CN_4H	single bond	H	CH_3	$COCH_3$
380	CN_4H	single bond	H	C_2H_5	$COCH_3$
381	CN_4H	CH_2CH_2-	H	H	$COCH_3$
382	CO_2H	single bond	H	CH_3	H
383	CO_2H	single bond	H	C_2H_5	H
384	CN_4H	CH_2CH_2-	H	H	H
385	CN_4H	single bond	H	CH_3	H
386	CN_4H	single bond	H	C_2H_5	H
387	CN_4H		*	H	$COCH_3$
388	CO_2H	single bond	H	H	$COCH_2Cl$

Ex: #	R5	A	B	E	P
389	CO_2H	single bond	H	H	COC_4H_9
390	CO_2H	single bond	H	CH_3	$COCH_3$
391	CO_2H	single bond	H	C_2H_5	$COCH_3$
392	CN_4H		*	H	H
393	CN_4H	single bond	H	H	$COCH_2Cl$
394	CN_4H	single bond	H	H	COC_4H_9
395	CN_4H	single bond	H	CH_3	$COCH_3$
396	CN_4H	single bond	H	C_2H_5	$COCH_3$
397	CN_4H		*	H	$COCH_3$
398	CO_2H	single bond	H	CH_3	H
399	CO_2H	single bond	H	C_2H_5	H
400	CN_4H		*	H	H
401	CN_4H	single bond	H	CH_3	H
402	CN_4H	single bond	H	C_2H_5	H

Ex: #	R_5	A	B	E	P
403	CN_4H		*	H	$COCH_3$
404	CO_2H	single bond	H	H	$COCH_2Cl$
405	CO_2H	single bond	H	H	COC_4H_9
406	CO_2H	single bond	H	CH_3	$COCH_3$
407	CO_2H	single bond	H	C_2H_5	$COCH_3$
408	CN_4H		*	H	H
409	CN_4H	single bond	H	H	$COCH_2Cl$
410	CN_4H	single bond	H	H	COC_4H_9
411	CN_4H	single bond	H	CH_3	$COCH_3$
412	CN_4H	single bond	H	C_2H_5	$COCH_3$
413	CN_4H		*	H	$COCH_3$
414	CO_2H	single bond	H	CH_3	H
415	CO_2H	single bond	H	C_2H_5	H
416	CN_4H		*	H	H

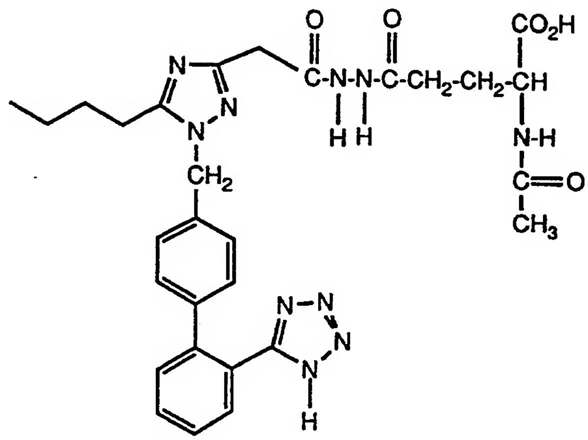
Ex: #	R_5	A	B	E	P
417	CN_4H	single bond	H	CH_3	H
418	CN_4H	single bond	H	C_2H_5	H
419	CN_4H		*	H	$COCH_3$
420	CN_4H	single bond	H	H	$COCH_2Cl$

Ex: #	R_5	A	B	E	P
421	CN_4H	single bond	H	H	COC_4H_9
422	CN_4H	single bond	H	CH_3	$COCH_3$
423	CN_4H	single bond	H	C_2H_5	$COCH_3$
424	CN_4H	$-CH_2CH_2-$ 	*	H	H
425	CN_4H	single bond	H	CH_3	H
426	CN_4H	single bond	H	C_2H_5	H

*** B is incorporated in A**

Another preferred class of specific conjugates of the invention is provided by conjugates formed from a biphenylmethyl 1H-substituted-1,2,4-triazole AII antagonist compound linked to a cleavable glutamyl residue. Each conjugate of this class contains a diamino linker moiety which connects a terminal carboxylic acid moiety on the triazole portion of the AII antagonist compound with a terminal carboxylic acid moiety on the gamma carbon of the cleavable glutamyl residue. Example #427 is a detailed description of a conjugate of this class. Other specific conjugates of Examples #428-#834, as shown in Table VI, may be prepared generally in accordance with the procedures of Example #427.

Example 427



N-acetyl-L-glutamic acid, 5-[5-butyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1,2,4-triazol-3-yl]acetylhydrazide

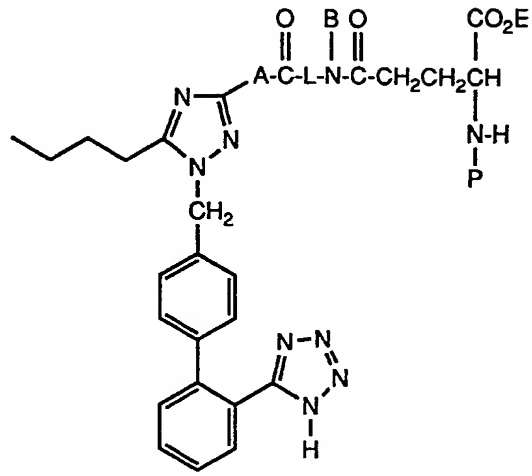
Step 1: Preparation of 5-[4'-[(5-butyl-3-hydrazinylcarbonyl-methyl-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole

Under nitrogen, 8.34 g (20 mmol) of the compound of Exampl 7 is dissolved in 200 mL of absolute methanol at -10°C (ice/methanol) and is treated dripwise with 3.0 g (25 mmol) of thionyl chloride. After the addition is complete, the reaction is allowed to warm to ambient temperature for 2 h prior to stirring at reflux overnight. All volitiles are removed in vacuo and the residue redissolved in 100 mL of methanol. Under nitrogen, 20 g (625 mmol) of anhydrous hydrazine is added and the reaction is stirred at reflux overnight. Concentration in vacuo gives the crude product; purification by silica gel chromatography provides 5-[4'-[(5-butyl-3-hydrazinocarbonylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

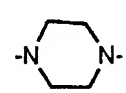
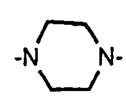
Step 2: Preparation of N-acetyl-L-glutamic acid, 5-[5-butyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1,2,4-triazol-3-yl]acetylhydrazide

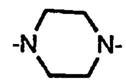
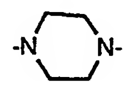
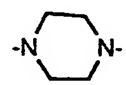
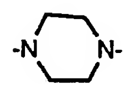
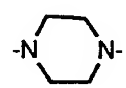
To a solution of 10.45 g (34.5 mmol) of N-Boc-L-glutamic acid-α-tertbutyl ester (BACHEM) in 100 mL of methylene chloride under nitrogen is added 3.5 g (17.0 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and filtered under nitrogen. The anhydride solution is then added to a solution of 6.42 g (14.9 mmol) of the compound of Example 20 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight and is concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500A) gives pure material by thin-layer chromatography (TLC). This material is redissolved in 100 mL of methylene chloride under nitrogen and cooled to 0°C prior to the addition of 135 mL of TFA. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated in vacuo. The crude product is dissolved in 80 mL of acetonitrile/water (1:1) and the pH is adjusted to 9 with 1 M K_2CO_3. The solution is cooled to 0°C and 1.1 mL (11 mmol) of acetic anhydride and 11 mL (11 mmol) of 1 M K_2CO_3 is added every 30 min for 5 h; during the course of this reaction the pH is maintained at 9 and the reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH was adjusted to 4 with 3 M HCl and the reaction concentrated to 300 mL. Purification by reverse phase chromatography (Waters Delta prep-3000) gives N-acetyl-L-glutamic acid, 5-[5-butyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1,2,4-traizol-3-yl]acetylhydrazide.

TABLE VI

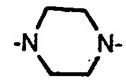
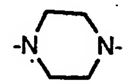
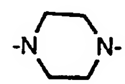
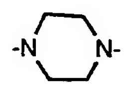
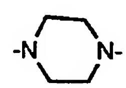
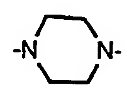
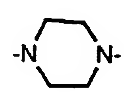
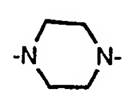


Ex. #	A	L	B	E	P
428	single bond	-NH-	H	H	$COCH_3$
429	single bond	-NH-	H	H	$COCH_2Cl$
430	single bond	-NH-	H	H	COC_4H_9
431	single bond	-NH-	H	CH_3	$COCH_3$
432	single bond	-NH-	H	C_2H_5	$COCH_3$
433	single bond	-NH-	H	H	H
434	single bond	-NH-	H	CH_3	H

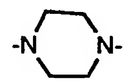
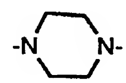
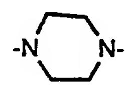
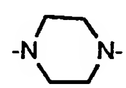
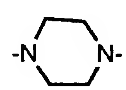
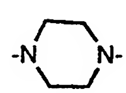
Ex. #	A	L	B	E	P
435	single bond	-NH-	H	C_2H_5	H
436	single bond	$-NHCH_2CH_2-$	H	H	$COCH_3$
437	single bond	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
438	single bond	$-NHCH_2CH_2-$	H	H	COC_4H_9
439	single bond	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
440	single bond	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
441	single bond	$-NHCH_2CH_2-$	H	H	H
442	single bond	$-NHCH_2CH_2-$	H	CH_3	H
443	single bond	$-NHCH_2CH_2-$	H	C_2H_5	H
444	single bond		*	H	$COCH_3$
445	single bond		H	H	$COCH_2Cl$

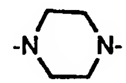
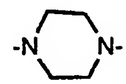
Ex. #	A	L	B	E	P
446	single bond		H	H	COC_4H_9
447	single bond		H	CH_3	$COCH_3$
448	single bond		H	C_2H_5	$COCH_3$
449	single bond		*	H	H
450	single bond		H	CH_3	H
451	single bond		H	C_2H_5	H
452	CH_2	-NH-	H	H	$COCH_2Cl$
453	CH_2	-NH-	H	H	COC_4H_9
454	CH_2	-NH-	H	CH_3	$COCH_3$

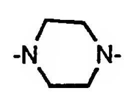
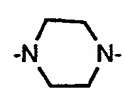
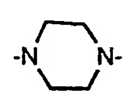
Ex. #	A	L	B	E	P
455	CH_2	-NH-	H	C_2H_5	$COCH_3$
456	CH_2	-NH-	H	H	H
457	CH_2	-NH-	H	CH_3	H
458	CH_2	-NH-	H	C_2H_5	H
459	CH_2	$-NHCH_2CH_2-$	H	H	$COCH_3$
460	CH_2	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
461	CH_2	$-NHCH_2CH_2-$	H	H	COC_4H_9
462	CH_2	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
463	CH_2	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
464	CH_2	$-NHCH_2CH_2-$	H	H	H
465	CH_2	$-NHCH_2CH_2-$	H	CH_3	H
466	CH_2	$-NHCH_2CH_2-$	H	C_2H_5	H

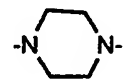
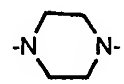
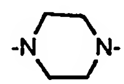
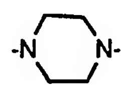
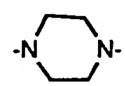
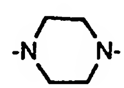
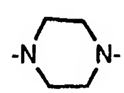
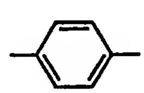
Ex. #	A	L	B	E	P
467	CH_2		*	H	$COCH_3$
468	CH_2		H	H	$COCH_2Cl$
469	CH_2		H	H	COC_4H_9
470	CH_2		H	CH_3	$COCH_3$
471	CH_2		H	C_2H_5	$COCH_3$
472	CH_2		*	H	H
473	CH_2		H	CH_3	H
474	CH_2		H	C_2H_5	H

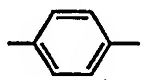
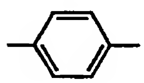
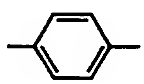
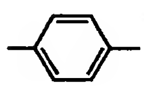
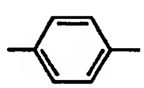
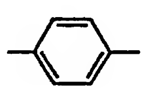
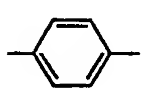
Ex. #	A	L	B	E	P
475	CH_2CH_2	-NH-	H	H	$COCH_3$
476	CH_2CH_2	-NH-	H	H	$COCH_2Cl$
477	CH_2CH_2	-NH-	H	H	COC_4H_9
478	CH_2CH_2	-NH-	H	CH_3	$COCH_3$
479	CH_2CH_2	-NH-	H	C_2H_5	$COCH_3$
480	CH_2CH_2	-NH-	H	H	H
481	CH_2CH_2	-NH-	H	CH_3	H
482	CH_2CH_2	-NH-	H	C_2H_5	H
483	CH_2CH_2	$-NHCH_2CH_2-$	H	H	$COCH_3$
484	CH_2CH_2	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
485	CH_2CH_2	$-NHCH_2CH_2-$	H	H	COC_4H_9
486	CH_2CH_2	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
487	CH_2CH_2	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$

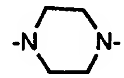
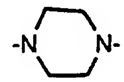
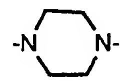
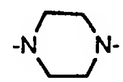
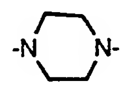
Ex. #	A	L	B	E	P
488	CH_2CH_2	$-NHCH_2CH_2-$	H	H	H
489	CH_2CH_2	$-NHCH_2CH_2-$	H	CH_3	H
490	CH_2CH_2	$-NHCH_2CH_2-$	H	C_2H_5	H
491	CH_2CH_2		*	H	$COCH_3$
492	CH_2CH_2		H	H	$COCH_2Cl$
493	CH_2CH_2		H	H	COC_4H_9
494	CH_2CH_2		H	CH_3	$COCH_3$
495	CH_2CH_2		H	C_2H_5	$COCH_3$
496	CH_2CH_2		*	H	H

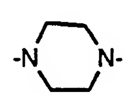
Ex. #	A	L	B	E	P
497	CH_2CH_2		H	CH_3	H
498	CH_2CH_2		H	C_2H_5	H
499	C_3H_6 (n)	-NH-	H	H	$COCH_3$
500	C_3H_6 (n)	-NH-	H	H	$COCH_2Cl$
501	C_3H_6 (n)	-NH-	H	H	COC_4H_9
502	C_3H_6 (n)	-NH-	H	CH_3	$COCH_3$
503	C_3H_6 (n)	-NH-	H	C_2H_5	$COCH_3$
504	C_3H_6 (n)	-NH-	H	H	H
505	C_3H_6 (n)	-NH-	H	CH_3	H
506	C_3H_6 (n)	-NH-	H	C_2H_5	H
507	C_3H_6 (n)	$-NHCH_2CH_2-$	H	H	$COCH_3$

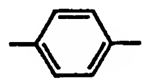
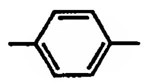
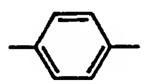
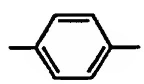
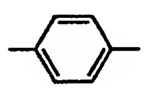
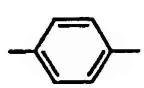
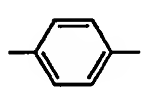
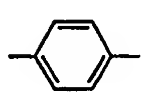
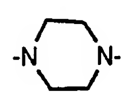
Ex. #	A	L	B	E	P
508	C_3H_6 (n)	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
509	C_3H_6 (n)	$-NHCH_2CH_2-$	H	H	COC_4H_9
510	C_3H_6 (n)	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
511	C_3H_6 (n)	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
512	C_3H_6 (n)	$-NHCH_2CH_2-$	H	H	H
513	C_3H_6 (n)	$-NHCH_2CH_2-$	H	CH_3	H
514	C_3H_6 (n)	$-NHCH_2CH_2-$	H	C_2H_5	H
515	C_3H_6 (n)		*	H	$COCH_3$
516	C_3H_6 (n)		H	H	$COCH_2Cl$
517	C_3H_6 (n)		H	H	COC_4H_9

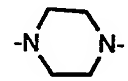
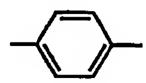
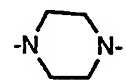
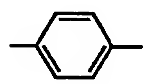
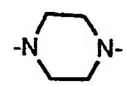
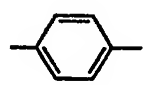
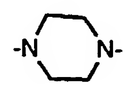
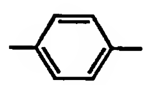
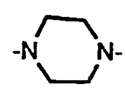
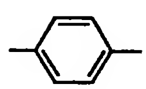
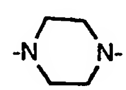
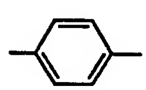
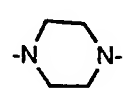
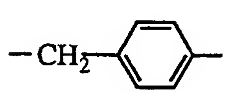
Ex. #	A	L	B	E	P
540	C_4H_8 (n)		H	H	$COCH_2Cl$
541	C_4H_8 (n)		H	H	COC_4H_9
542	C_4H_8 (n)		H	CH_3	$COCH_3$
543	C_4H_8 (n)		H	C_2H_5	$COCH_3$
544	C_4H_8 (n)		*	H	H
545	C_4H_8 (n)		H	CH_3	H
546	C_4H_8 (n)		H	C_2H_5	H
547		-NH-	H	H	$COCH_3$

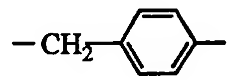
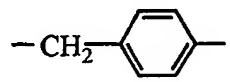
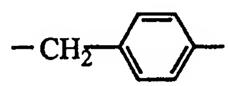
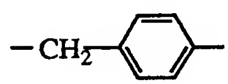
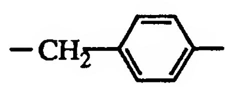
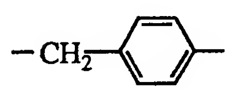
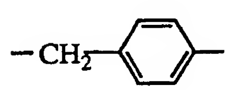
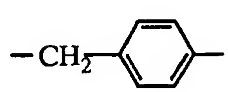
Ex. #	A	L	B	E	P
548		-NH-	H	H	$COCH_2Cl$
549		-NH-	H	H	COC_4H_9
550		-NH-	H	CH_3	$COCH_3$
551		-NH-	H	C_2H_5	$COCH_3$
552		-NH-	H	H	H
553		-NH-	H	CH_3	H
554		-NH-	H	C_2H_5	H
555		$-NHCH_2CH_2-$	H	H	$COCH_3$

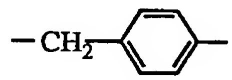
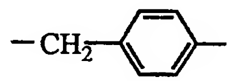
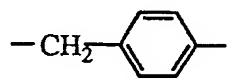
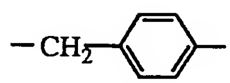
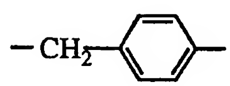
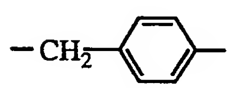
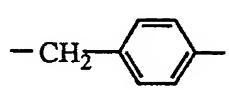
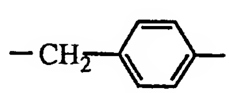
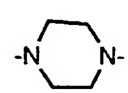
Ex. #	A	L	B	E	P
518	C_3H_6 (n)		H	CH_3	$COCH_3$
519	C_3H_6 (n)		H	C_2H_5	$COCH_3$
520	C_3H_6 (n)		*	H	H
521	C_3H_6 (n)		H	CH_3	H
522	C_3H_6 (n)		H	C_2H_5	H
523	C_4H_8 (n)	-NH-	H	H	$COCH_3$
524	C_4H_8 (n)	-NH-	H	H	$COCH_2Cl$
525	C_4H_8 (n)	-NH-	H	H	COC_4H_9
526	C_4H_8 (n)	-NH-	H	CH_3	$COCH_3$
527	C_4H_8 (n)	-NH-	H	C_2H_5	$COCH_3$

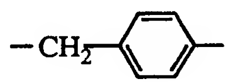
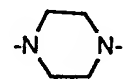
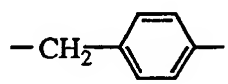
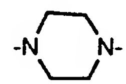
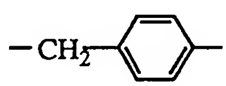
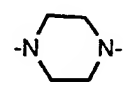
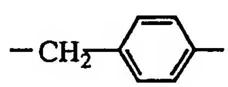
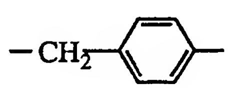
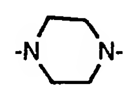
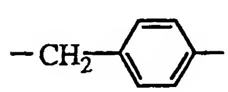
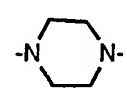
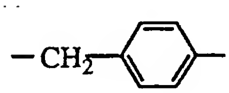
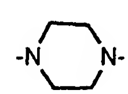
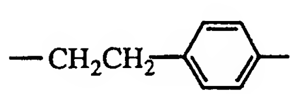
Ex. #	A	L	B	E	P
528	C_4H_8 (n)	-NH-	H	H	H
529	C_4H_8 (n)	-NH-	H	CH_3	H
530	C_4H_8 (n)	-NH-	H	C_2H_5	H
531	C_4H_8 (n)	$-NHCH_2CH_2-$	H	H	$COCH_3$
532	C_4H_8 (n)	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
533	C_4H_8 (n)	$-NHCH_2CH_2-$	H	H	COC_4H_9
534	C_4H_8 (n)	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
535	C_4H_8 (n)	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
536	C_4H_8 (n)	$-NHCH_2CH_2-$	H	H	H
537	C_4H_8 (n)	$-NHCH_2CH_2-$	H	CH_3	H
538	C_4H_8 (n)	$-NHCH_2CH_2-$	H	C_2H_5	H
539	C_4H_8 (n)		*	H	$COCH_3$

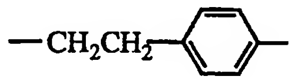
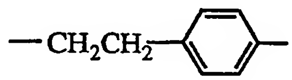
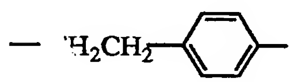
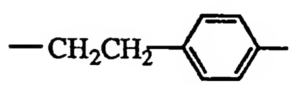
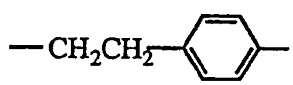
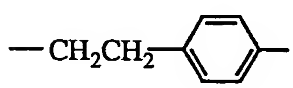
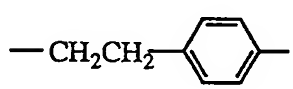
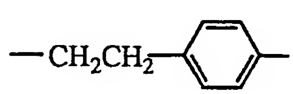
Ex. #	A	L	B	E	P
556		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
557		$-NHCH_2CH_2-$	H	H	COC_4H_9
558		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
559		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
560		$-NHCH_2CH_2-$	H	H	H
561		$-NHCH_2CH_2-$	H	CH_3	H
562		$-NHCH_2CH_2-$	H	C_2H_5	H
563			*	H	$COCH_3$

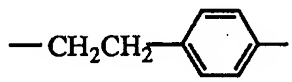
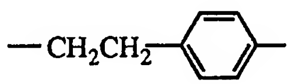
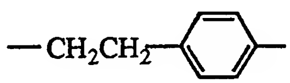
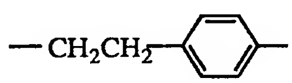
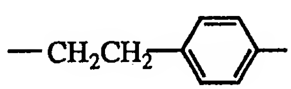
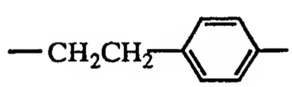
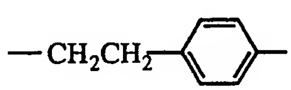
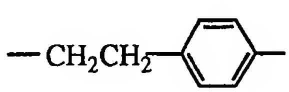
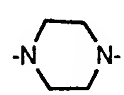
Ex. #	A	L	B	E	P
564			H	H	$COCH_2Cl$
565			H	H	COC_4H_9
566			H	CH_3	$COCH_3$
567			H	C_2H_5	$COCH_3$
568			*	H	H
569			H	CH_3	H
570			H	C_2H_5	H
571		-NH-	H	H	$COCH_3$

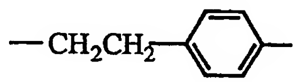
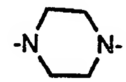
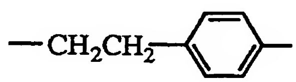
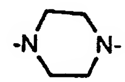
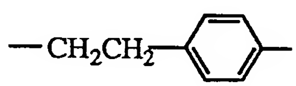
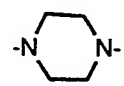
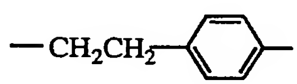
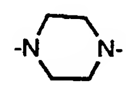
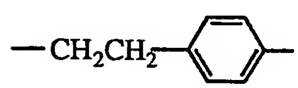
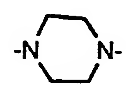
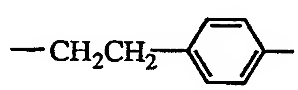
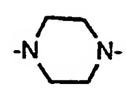
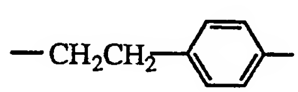
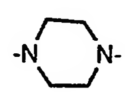
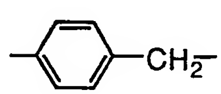
Ex. #	A	L	B	E	P
572		-NH-	H	H	$COCH_2Cl$
573		-NH-	H	H	COC_4H_9
574		-NH-	H	CH_3	$COCH_3$
575		-NH-	H	C_2H_5	$COCH_3$
576		-NH-	H	H	H
577		-NH-	H	CH_3	H
578		-NH-	H	C_2H_5	H
579		$-NHCH_2CH_2-$	H	H	$COCH_3$

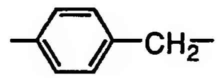
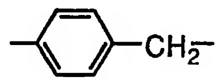
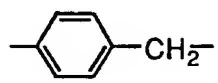
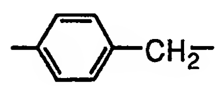
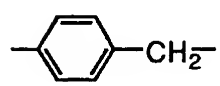
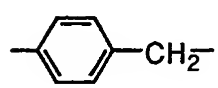
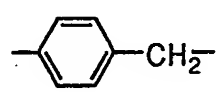
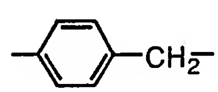
Ex. #	A	L	B	E	P
580		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
581		$-NHCH_2CH_2-$	H	H	COC_4H_9
582		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
583		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
584		$-NHCH_2CH_2-$	H	H	H
585		$-NHCH_2CH_2-$	H	CH_3	H
586		$-NHCH_2CH_2-$	H	C_2H_5	H
587			*	H	$COCH_3$

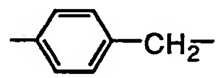
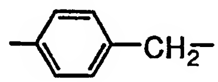
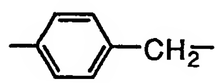
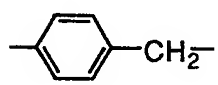
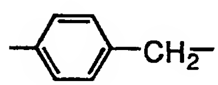
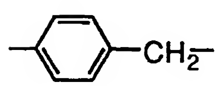
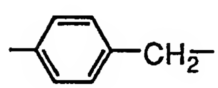
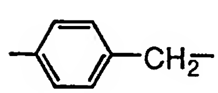
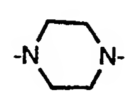
Ex. #	A	L	B	E	P
588			H	H	$COCH_2Cl$
589			H	H	COC_4H_9
590			H	CH_3	$COCH_3$
591			H	C_2H_5	$COCH_3$
592			*	H	H
593			H	CH_3	H
594			H	C_2H_5	H
595		-NH-	H	H	$COCH_3$

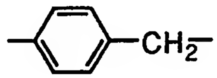
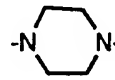
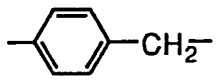
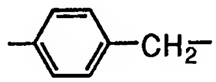
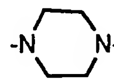
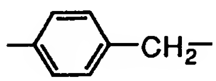
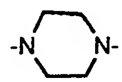
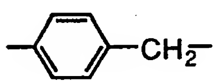
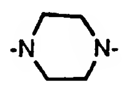
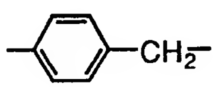
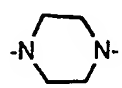
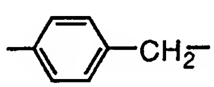
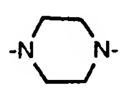
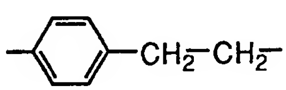
Ex. #	A	L	B	E	P
596		-NH-	H	H	$COCH_2Cl$
597		-NH-	H	H	COC_4H_9
598		-NH-	H	CH_3	$COCH_3$
599		-NH-	H	C_2H_5	$COCH_3$
600		-NH-	H	H	H
601		-NH-	H	CH_3	H
602		-NH-	H	C_2H_5	H
603		$-NHCH_2CH_2-$	H	H	$COCH_3$

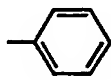
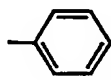
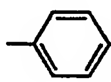
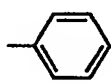
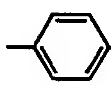
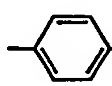
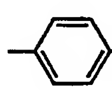
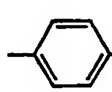
Ex. #	A	L	B	E	P
604		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
605		$-NHCH_2CH_2-$	H	H	COC_4H_9
606		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
607		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
608		$-NHCH_2CH_2-$	H	H	H
609		$-NHCH_2CH_2-$	H	CH_3	H
610		$-NHCH_2CH_2-$	H	C_2H_5	H
611			*	H	$COCH_3$

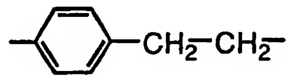
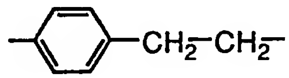
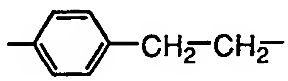
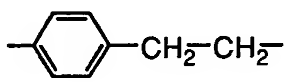
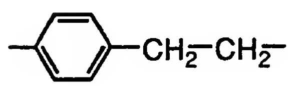
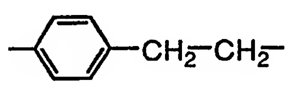
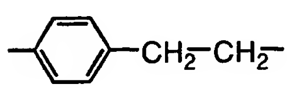
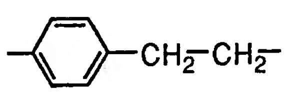
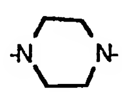
Ex. #	A	L	B	E	P
612			H	H	$COCH_2Cl$
613			H	H	COC_4H_9
614			H	CH_3	$COCH_3$
615			H	C_2H_5	$COCH_3$
616			*	H	H
617			H	CH_3	H
618			H	C_2H_5	H
619		-NH-	H	H	$COCH_3$

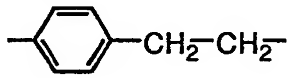
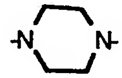
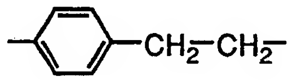
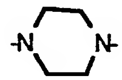
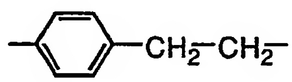
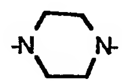
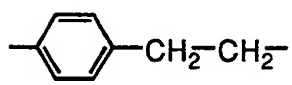
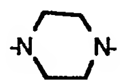
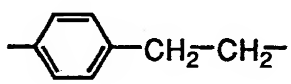
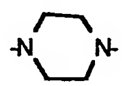
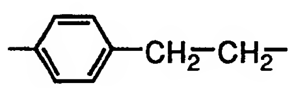
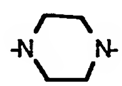
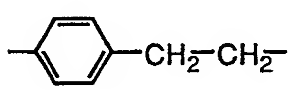
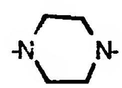
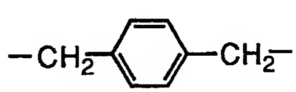
Ex. #	A	L	B	E	P
620		-NH-	H	H	$COCH_2Cl$
621		-NH-	H	H	COC_4H_9
622		-NH-	H	CH_3	$COCH_3$
623		-NH-	H	C_2H_5	$COCH_3$
624		-NH-	H	H	H
625		-NH-	H	CH_3	H
626		-NH-	H	C_2H_5	H
627		$-NHCH_2CH_2-$	H	H	$COCH_3$

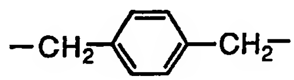
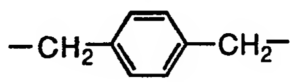
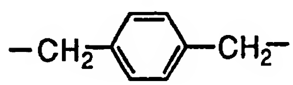
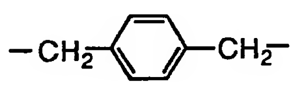
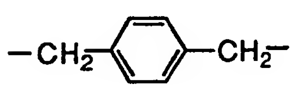
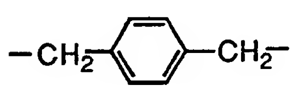
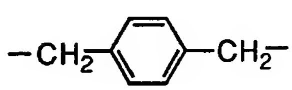
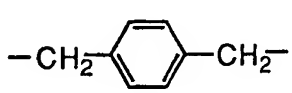
Ex. #	A	L	B	E	P
628		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
629		$-NHCH_2CH_2-$	H	H	COC_4H_9
630		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
631		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
632		$-NHCH_2CH_2-$	H	H	H
633		$-NHCH_2CH_2-$	H	CH_3	H
634		$-NHCH_2CH_2-$	H	C_2H_5	H
635			*	H	$COCH_3$

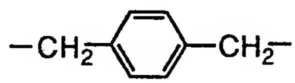
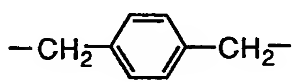
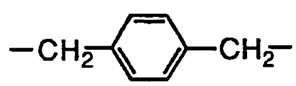
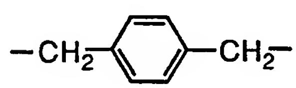
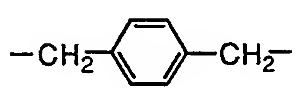
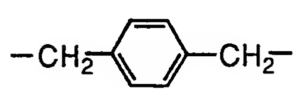
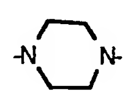
Ex. #	A	L	B	E	P
636			H	H	$COCH_2Cl$
637			H	H	COC_4H_9
638			H	CH_3	$COCH_3$
639			H	C_2H_5	$COCH_3$
640			*	H	H
641			H	CH_3	H
642			H	C_2H_5	H
643		–NH–	H	H	$COCH_3$

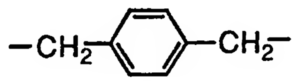
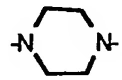
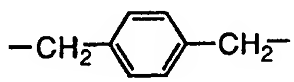
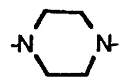
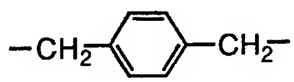
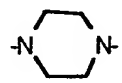
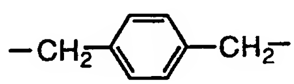
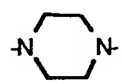
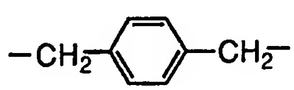
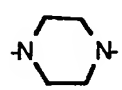
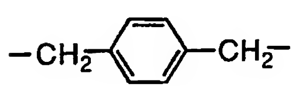
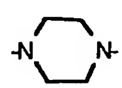
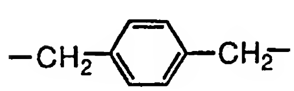
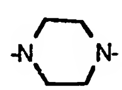
Ex. #	A	L	B	E	P
644	$-CH_2-CH_2-$	-NH-	H	H	$COCH_2Cl$
645	$-CH_2-CH_2-$	-NH-	H	H	COC_4H_9
646	$-CH_2-CH_2-$	-NH-	H	CH_3	$COCH_3$
647	$-CH_2-CH_2-$	-NH-	H	C_2H_5	$COCH_3$
648	$-CH_2-CH_2-$	-NH-	H	H	H
649	$-CH_2-CH_2-$	-NH-	H	CH_3	H
650	$-CH_2-CH_2-$	-NH-	H	C_2H_5	H
651	$-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	H	$COCH_3$

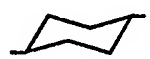
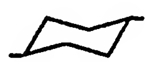
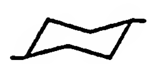
Ex. #	A	L	B	E	P
652		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
653		$-NHCH_2CH_2-$	H	H	COC_4H_9
654		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
655		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
656		$-NHCH_2CH_2-$	H	H	H
657		$-NHCH_2CH_2-$	H	CH_3	H
658		$-NHCH_2CH_2-$	H	C_2H_5	H
659			*	H	$COCH_3$

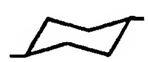
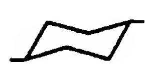
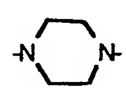
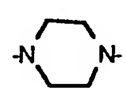
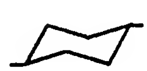
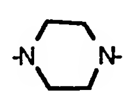
Ex. #	A	L	B	E	P
660			H	H	$COCH_2Cl$
661			H	H	COC_4H_9
662			H	CH_3	$COCH_3$
663			H	C_2H_5	$COCH_3$
664			*	H	H
665			H	CH_3	H
666			H	C_2H_5	H
667		-NH-	H	H	$COCH_3$

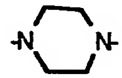
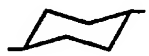
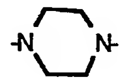
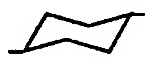
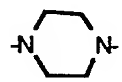
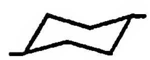
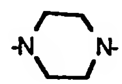
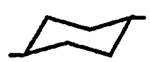
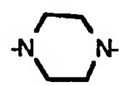
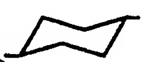
Ex. #	A	L	B	E	P
668		-NH-	H	H	$COCH_2Cl$
669		-NH-	H	H	COC_4H_9
670		-NH-	H	CH_3	$COCH_3$
671		-NH-	H	C_2H_5	$COCH_3$
672		-NH-	H	H	H
673		-NH-	H	CH_3	H
674		-NH-	H	C_2H_5	H
675		$-NHCH_2CH_2-$	H	H	$COCH_3$

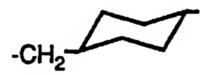
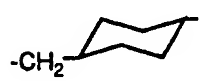
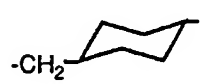
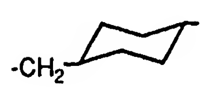
Ex. #	A	L	B	E	P
676		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
677		$-NHCH_2CH_2-$	H	H	COC_4H_9
678		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
679		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
680		$-NHCH_2CH_2-$	H	H	H
681		$-NHCH_2CH_2-$	H	CH_3	H
682		$-NHCH_2CH_2-$	H	C_2H_5	H
683			*	H	$COCH_3$

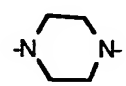
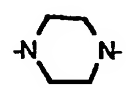
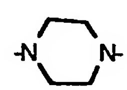
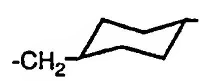
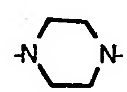
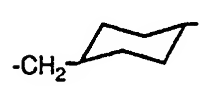
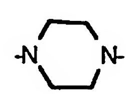
Ex. #	A	L	B	E	P
684			H	H	$COCH_2Cl$
685			H	H	COC_4H_9
686			H	CH_3	$COCH_3$
687			H	C_2H_5	$COCH_3$
688			*	H	H
689			H	CH_3	H
690			H	C_2H_5	H
691		-NH-	H	H	$COCH_3$

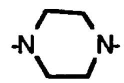
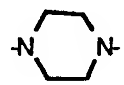
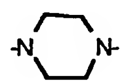
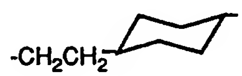
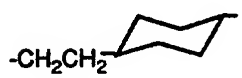
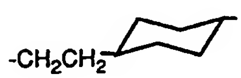
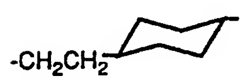
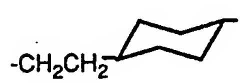
Ex. #	A	L	B	E	P
692		-NH-	H	H	$COCH_2Cl$
693		-NH-	H	H	COC_4H_9
694		-NH-	H	CH_3	$COCH_3$
695		-NH-	H	C_2H_5	$COCH_3$
696		-NH-	H	H	H
697		-NH-	H	CH_3	H
698		-NH-	H	C_2H_5	H
699		$-NHCH_2CH_2-$	H	H	$COCH_3$
700		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$

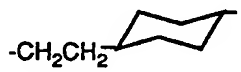
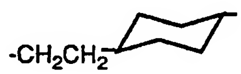
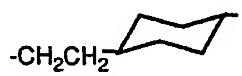
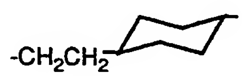
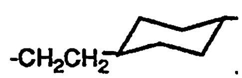
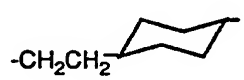
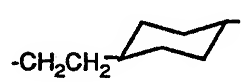
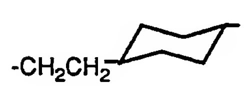
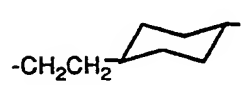
Ex. #	A	L	B	E	P
701		$-NHCH_2CH_2-$	H	H	COC_4H_9
702		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
703		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
704		$-NHCH_2CH_2-$	H	H	H
705		$-NHCH_2CH_2-$	H	CH_3	H
706		$-NHCH_2CH_2-$	H	C_2H_5	H
707			*	H	$COCH_3$
708			H	H	$COCH_2Cl$
709			H	H	COC_4H_9

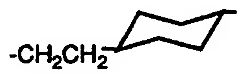
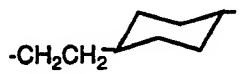
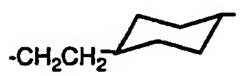
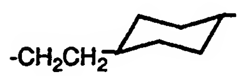
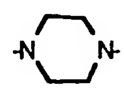
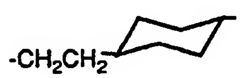
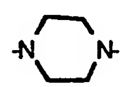
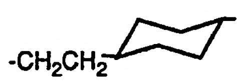
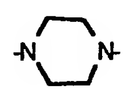
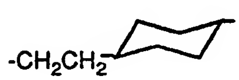
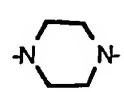
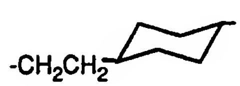
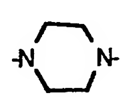
Ex. #	A	L	B	E	P
710			H	CH_3	$COCH_3$
711			H	C_2H_5	$COCH_3$
712			*	H	H
713			H	CH_3	H
714			H	C_2H_5	H
715	-CH_2- 	-NH-	H	H	$COCH_3$
716	-CH_2- 	-NH-	H	H	$COCH_2Cl$
717	-CH_2- 	-NH-	H	H	COC_4H_9
718	-CH_2- 	-NH-	H	CH_3	$COCH_3$

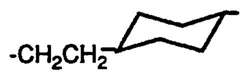
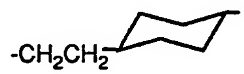
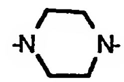
Ex. #	A	L	B	E	P
719		-NH-	H	C_2H_5	$COCH_3$
720		-NH-	H	H	H
721		-NH-	H	CH_3	H
722		-NH-	H	C_2H_5	H
723		$-NHCH_2CH_2-$	H	H	$COCH_3$
724		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
725		$-NHCH_2CH_2-$	H	H	COC_4H_9
726		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
727		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$

Ex. #	A	L	B	E	P
728		$-NHCH_2CH_2-$	H	H	H
729		$-NHCH_2CH_2-$	H	CH_3	H
730		$-NHCH_2CH_2-$	H	C_2H_5	H
731			*	H	$COCH_3$
732			H	H	$COCH_2Cl$
733			H	H	COC_4H_9
734			H	CH_3	$COCH_3$
735			H	C_2H_5	$COCH_3$

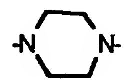
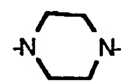
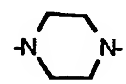
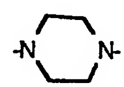
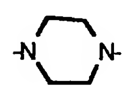
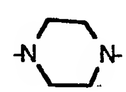
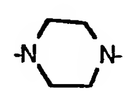
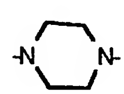
Ex. #	A	L	B	E	P
736			*	H	H
737			H	CH_3	H
738			H	C_2H_5	H
739		-NH-	H	H	$COCH_3$
740		-NH-	H	H	$COCH_2Cl$
741		-NH-	H	H	COC_4H_9
742		-NH-	H	CH_3	$COCH_3$
743		-NH-	H	C_2H_5	$COCH_3$

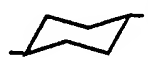
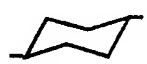
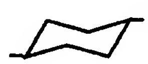
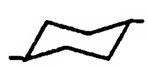
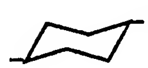
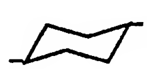
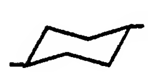
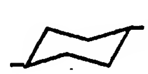
Ex. #	A	L	B	E	P
744		-NH-	H	H	H
745		-NH-	H	CH_3	H
746		-NH-	H	C_2H_5	H
747		$-NHCH_2CH_2-$	H	H	$COCH_3$
748		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
749		$-NHCH_2CH_2-$	H	H	COC_4H_9
750		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
751		$-NHCH_2CH_2-$	H	C_2H_5	C OCH_3
752		$-NHCH_2CH_2-$	H	H	H

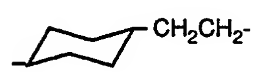
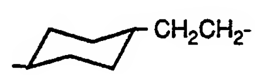
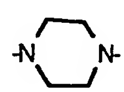
Ex. #	A	L	B	E	P
753		$-NHCH_2CH_2-$	H	CH_3	H
754		$-NHCH_2CH_2-$	H	C_2H_5	H
755			*	H	$COCH_3$
756			H	H	$COCH_2Cl$
757			H	H	COC_4H_9
758			H	CH_3	$COCH_3$
759			H	C_2H_5	$COCH_3$
760			*	H	H

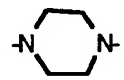
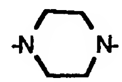
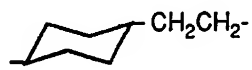
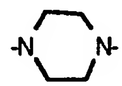
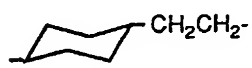
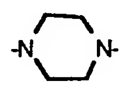
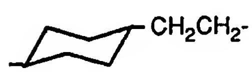
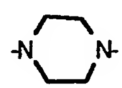
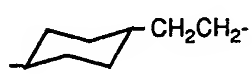
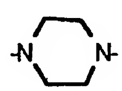
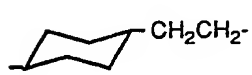
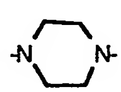
Ex. #	A	L	B	E	P
761			H	CH_3	H
762			H	C_2H_5	H
763		-NH-	H	H	$COCH_3$
764		-NH-	H	H	$COCH_2Cl$
765		-NH-	H	H	COC_4H_9
766		-NH-	H	CH_3	$COCH_3$
767		-NH-	H	C_2H_5	$COCH_3$
768		-NH-	H	H	H

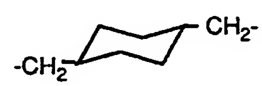
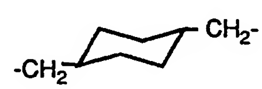
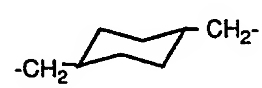
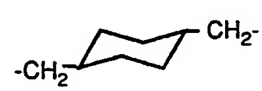
Ex. #	A	L	B	E	P
769		-NH-	H	CH_3	H
770		-NH-	H	C_2H_5	H
771		$-NHCH_2CH_2-$	H	H	$COCH_3$
772		-NH-	H	H	$COCH_2Cl$
773		-NH-	H	H	COC_4H_9
774		-NH-	H	CH_3	$COCH_3$
775		-NH-	H	C_2H_5	$COCH_3$
776		$-NHCH_2CH_2-$	H	H	H
777		$-NHCH_2CH_2-$	H	CH_3	H
778		$-NHCH_2CH_2-$	H	C_2H_5	H

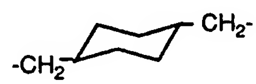
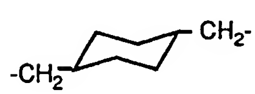
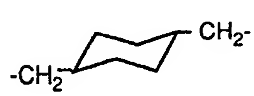
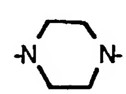
Ex. #	A	L	B	E	P
779			*	H	$COCH_3$
780			H	H	$COCH_2Cl$
781			H	H	COC_4H_9
782			H	CH_3	$COCH_3$
783			C_2H_5		$COCH_3$
784			*	H	H
785			H	CH_3	H
786			H	C_2H_5	H

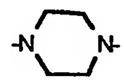
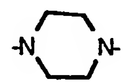
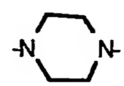
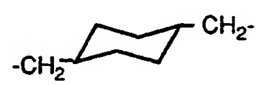
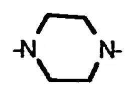
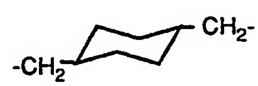
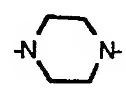
Ex. #	A	L	B	E	P
787	 CH_2CH_2-	-NH-	H	H	$COCH_3$
788	 CH_2CH_2-	-NH-	H	H	$COCH_2Cl$
789	 CH_2CH_2-	-NH-	H	H	COC_4H_9
790	 CH_2CH_2-	-NH-	H	CH_3	$COCH_3$
791	 CH_2CH_2-	-NH-	H	C_2H_5	$COCH_3$
792	 CH_2CH_2-	-NH-	H	H	H
793	 CH_2CH_2-	-NH-	H	CH_3	H
794	 CH_2CH_2-	-NH-	H	C_2H_5	H
795	 CH_2CH_2-	$-NHCH_2CH_2-$	H	H	$COCH_3$

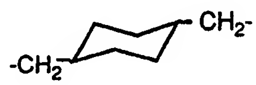
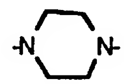
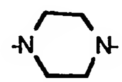
Ex. #	A	L	B	E	P
796		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
797		$-NHCH_2CH_2-$	H	H	COC_4H_9
798		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
799		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
800		$-NHCH_2CH_2-$	H	H	H
801		$-NHCH_2CH_2-$	H	CH_3	H
802		$-NHCH_2CH_2-$	H	C_2H_5	H
803			*	H	$COCH_3$

Ex. #	A	L	B	E	P
804			H	H	$COCH_2Cl$
805			H	H	COC_4H_9
806			H	CH_3	$COCH_3$
807			H	C_2H_5	$COCH_3$
808			*	H	H
809			H	CH_3	H
810			H	C_2H_5	H
811		-NH-	H	H	$COCH_3$

Ex. #	A	L	B	E	P
812		–NH–	H	H	$COCH_2Cl$
813		–NH–	H	H	COC_4H_9
814		–NH–	H	CH_3	$COCH_3$
815		–NH–	H	C_2H_5	C OCH_3
816		–NH–	H	H	H
817		–NH–	H	CH_3	H
818		–NH–	H	C_2H_5	H
819		$-NHCH_2CH_2-$	H	H	$COCH_3$

Ex. #	A	L	B	E	P
820		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
821		$-NHCH_2CH_2-$	H	H	COC_4H_9
822		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
823		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
824		$-NHCH_2CH_2-$	H	H	H
825		$-NHCH_2CH_2-$	H	CH_3	H
826		$-NHCH_2CH_2-$	H	C_2H_5	H
827			*	H	$COCH_3$

Ex. #	A	L	B	E	P
828			H	H	$COCH_2Cl$
829			H	H	COC_4H_9
830			H	CH_3	$COCH_3$
831			H	C_2H_5	$COCH_3$
832			*	H	H

Ex. #	A	L	B	E	P
833			H	CH_3	H
834			H	C_2H_5	H

BIOLOGICAL EVALUATION

In order to identify suitable angiotension II antagonists for use as the first component of the conjugate of the invention, certain compounds of Examples 1-17 were evaluated variously in three biological assays (Assays "A", "B" and "C"). In a fourth assay, blood-pressue lowering effects of conjugate of the invention of Example 18 were evaluated (Assay "D").

Assay A: Angiotensin II Binding Activity

Compounds of Formula I were tested for ability to bind to the smooth muscle angiotensin II receptor using a rat uterine membrane preparation. Angiotensin II (AII) was purchased from Peninsula Labs. ^{125}I-angiotensin II (specific activity of 2200 Ci/mmol) was purchased from Du Pont-New England Nuclear. Other chemicals were obtained from Sigma Chemical Co. This assay was carried out according to the method of Douglas et al [Endocrinology, 106, 120-124 (1980)]. Rat uterine membranes were prepared from fresh tissue. All procedures were carried out at 4°C. Uteri were stripped of fat and homogenized in phosphate-buffered saline at pH 7.4 containing 5 mM EDTA. The homogenate was centrifuged at 1500 x g for 20 min., and the supernatant was recentrifuged at 100,000 x g for 60 min. The pellet was resuspended in buffer consisting of 2 mM EDTA and 50 mM Tris-HCl (pH 7.5) to a final protein concentration of 4 mg/ml. Assay tubes were charged with 0.25 ml of a solution containing 5 mM $MgCl_2$, 2 mM EDTA, 0.5% bovine serum albumin, 50 mM Tris-HCl, pH 7.5 and ^{125}I-AII (approximately 10^5 cpm) in the absence or in the presence of unlabelled ligand. The reaction was initiated by the addition of membrane protein and the mixture was incubated at 25°C for 60 min. The incubation was terminated with ice-cold 50 mM Tris-HCl (pH 7.5) and the mixture was filtered to separate membrane-bound labelled peptide from the free ligand. The incubation tube and filter were washed

with ice-cold buffer. Filters were assayed for radioactivity in a Micromedic gamma counter. Nonspecific binding was defined as binding in the presence of 10 µM of unlabelled AII. Specific binding was calculated as total binding minus nonspecific binding. The receptor binding affinity of an AII antagonist compound was indicated by the concentration (IC_{50}) of the tested AII antagonist which gives 50% displacement of the total specifically bound ^{125}I-AII from the high affinity AII receptor. Binding data were analyzed by a nonlinear least-squares curve fitting program. Results are reported in Table VI.

Assay B: In Vitro Vascular Smooth Muscle-Response for AII

Compounds of Formula I were tested for antagonist activity in rabbit aortic rings. Male New Zealand white rabbits (2-2.5 kg) were sacrificed using an overdose of pentobarbital and exsanguinated via the carotid arteries. The thoracic aorta was removed, cleaned of adherent fat and connective tissue and then cut into 3-mm ring segments. The endothelium was removed from the rings by gently sliding a rolled-up piece of filter paper into the vessel lumen. The rings were then mounted in a water-jacketed tissue bath, maintained at 37°C, between moveable and fixed ends of a stainless steel wire with the moveable end attached to an FT03 Grass transducer coupled to a Model 7D Grass Polygraph for recording isometric force responses. The bath was filled with 20 ml of oxygenated (95% oxygen/5% carbon dioxide) Krebs solution of the following composition (nM): 130 NaCl, 15 $NaHCO_3$, 15 KCl, 1.2 NaH_2PO_4, 1.2 $MgSO_4$, 2.5 $CaCl_2$, and 11.4 glucose. The preparations were equilibrated for one hour before approximately one gram of passive tension was placed on the rings. Angiotensin II concentration-response curves were then recorded (3 X 10^{-10} to 1 X 10^{-5} M). Each concentration of AII was allowed to elicit its maximal contraction, and then AII was washed out repeatedly for 30 minutes before rechallenging with a higher concentration of AII. Aorta rings were exposed to

the test antagonist at 10^{-5} M for 5 minutes before challenging with AII. Adjacent segments of the same aorta ring were used for all concentration-response curves in the presence or absence of the test antagonist. The effectiveness of the test compound was expressed in terms of pA_2 values and were calculated according to H.O. Schild [Br. J. Pharmacol. Chemother., 2,189-206 (1947)]. The pA_2 value is the concentration of the antagonist which increases the EC_{50} value for AII by a factor of 2. Each test antagonist was evaluated in aorta rings from two rabbits. Results are reported in Table VI.

Assay C: In Vivo Intraduodenal Pressor Assay Response for AII Antagonists

Male Sprague-Dawley rats weighing 225-300 grams were anesthetized with Inactin (100 mg/kg, i.p.) and catheters were implanted into the trachea, femoral artery, femoral vein and duodenum. Arterial pressure was recorded from the femoral artery catheter on a Gould chart recorder (Gould, Cleveland, OH). The femoral vein catheter was used for injections of angiotensin II, mecamylamine and atropine. The tracheal catheter allow for airway patency, and the duodenal catheter was used for intraduodenal (i.d.) administration of test compounds. After surgery, the rats were allowed to equilibrate for 30 minutes. Mecamylamine (3 mg/kg, 0.3 ml/kg) and atropine (400 ug/kg, 0.3 ml/kg) were then given i.v. to produce ganglion blockade. These compounds were administered every 90 minutes throughout the test procedure. Angiotensin II was given in bolus does i.v. (30 ng/kg in saline with 0.5% bovine serum albumin, 0.1 ml/kg) every 10 minutes three times or until the increase in arterial pressure produced was within 3 mmHg for two consecutive AII injections. The last two AII injections were averaged and were taken as the control AII pressor response. Ten minutes after the final control AII injection, the test compound of Formula I (dissolved in sodium bicarbonate) was administered i.d. at a dose of 30

or 100 mg/kg in a volume of 0.2 ml. Angiotensin II injections were then given 5, 10, 20, 30, 45, 60, 75, 90, and 120 minutes after administration of the test compound and response of arterial pressure was monitored. The response to AII was calculated as percent of the control response and then the percent inhibition is calculated as 100 minus the percent control response. Duration of action of a test compound was defined as the time from peak percent inhibition to 50% of peak. One compound at one dose was tested in each rat. Each test compound was tested in two rats and the values for the two rats were averaged. Results are reported in Table IV.

TABLE IV

In Vivo and In Vitro Angiotensin II Activity of Compounds of the Invention

Test Compound Example #	[1]Assay A IC_{50} (nM)	[2]Assay B pA_2	Dose (mg/kg)	[3]Assay C Inhibition (%)	Duration (min.)
1	NT	NT	NT	NT	NT
2	95	7.37/7.59	10	95	60
			30	98	90-120
3	5.4	8.70 ± 0.2	10	50	>180
			30	100	200^+
4	NT	NT	NT	NT	NT
5	200	7.48/6.91	30	38	20-30
6	1300	6.55/6.82	100	90	120
7	84	8.01/8.05	30	90	130
8	17,000	NT	NT	NT	NT
9	700	6.67/6.12	30	80	75
			100	100	130
10	4.9	8.19/7.59	3	86	100
			30	100	240
11	160	6.45/6.77	NT	NT	NT
12	6.0	8.66/8.59	NT	NT	NT
13	17	8.70/8.85	NT	NT	NT
14	7.2	8.84/8.71	NT	NT	NT
15	16	8.31/8.30	NT	NT	NT
16	6.4	8.95/9.24	NT	NT	NT
17	4.0	8.64/8.40	NT	NT	NT
18	970	6.14/6.09	NT	NT	NT
19	12,000	5.18/5.35	NT	NT	NT

Test Compound Example #	[1]Assay A IC_{50} (nM)	[2]Assay B pA_2	Dose (mg/kg)	[3]Assay C Inhibition (%)	Duration (min.)
20	78,000	5.89/5.99	100	10	45
21	87	7.71.7.21	NT	NT	NT
22	460	6.60/6.46	NT	NT	NT
23	430	6.48/7.15	NT	NT	NT
24	10	7.56/7.73	NT	NT	NT
25	480	6.80/6.73	NT	NT	NT
26	3.2	9.83/9.66	10	50	>180
27	180	NT	NT	NT	NT
28	570	5.57/6.00	NT	NT	NT
29	160	NT	NT	NT	NT
30	22	7.73/7.88	30	50	>180
31	14	NT	NT	NT	NT
32	16	7.68/7.29	NT	NT	NT
33	630	6.73/6.36	NT	NT	NT
34	640	5.34/5.69	NT	NT	NT
35	41	7.25/7.47	NT	NT	NT
36	1400	5.92/5.68	NT	NT	NT
37	340	6.90/6.85	NT	NT	NT
38	10	7.82/8.36	NT	NT	NT
39	10	7.88/7.84	NT	NT	NT
40	83	7.94/7.61	NT	NT	NT
41	3700	5.68/5.96	NT	NT	NT
42	370	6.56/6.26	NT	NT	NT
43	19	8.97/8.61	NT	NT	NT
44	16	8.23/7.70	NT	NT	NT
45	4.4	8.41/8.24	NT	NT	NT
46	110	6.80/6.64	NT	NT	NT

Test Compound Duration Example # (min.)	[1]Assay A IC_{50} (nM)	[2]Assay B pA_2	Dose (mg/kg)	[3]Assay C Inhibition (%)	
47	21	7.85/7.58	NT	NT	NT
48	680	6.27/6.75	NT	NT	NT
49	120	7.06/7.07	NT	NT	NT
50	54	7.71/7.89	NT	NT	NT
51	8.7	8.39/8.51	NT	NT	NT
52	100	8.14/8.12	NT	NT	NT
53	65	7.56/7.83	NT	NT	NT
54	3100	6.02	NT	NT	NT
55	80	6.56/7.13	NT	NT	NT
56	5.0	9.04/8.35	NT	NT	NT
57	2300	6.00	NT	NT	NT
58	140	6.45/6.57	NT	NT	NT
59	120	7.23/7.59	NT	NT	NT
60	2200	6.40/6.03	NT	NT	NT
61	110	7.29/7.70	NT	NT	NT
62	26	8.69/8.61	NT	NT	NT
63	61	7.77/7.67	NT	NT	NT
64	54	7.00/6.77	NT	NT	NT
65	23	7.85/7.75	NT	NT	NT
66	12	9.34/8.58	NT	NT	NT
67	3100	5.88/5.78	NT	NT	NT
68	8.6	8.19/8.65	NT	NT	NT
69	15	7.80/8.28	NT	NT	NT
70	44	7.71/8.05	NT	NT	NT
71	12,000	*	NT	NT	NT
72	83	6.11/6.10	NT	NT	NT
73	790	7.65/7.46	NT	NT	NT

Test Compound Example #	[1]Assay A IC_{50} (nM)	[2]Assay B pA_2	Dose (mg/kg)	[3]Assay C Inhibition (%)	Duration (min.)
74	6.5	8.56/8.39	NT	NT	NT
75	570	6.00/5.45	NT	NT	NT
76	5400	5.52/5.78	NT	NT	NT
77	15,000	5.77	NT	NT	NT
78	480	6.41/6.35	NT	NT	NT

NT = NOT TESTED

*Antagonist activity not observed up to 10 μM of test compound.

[1]Assay A: Angiotensin II Binding Activity

[2]Assay B: In Vitro Vascular Smooth Muscle Response

[3]Assays C/D: In Vivo Pressor Response (test compounds administered intraduodenally, except for compounds of Examples #3, #26 and #30 which were given intragastrically).

Assay D: *In Vivo* Effects of Chronic Infusion of Conjugate of the Invention

A conjugate of the invention as synthesized in Example 79 was evaluated biologically by in vivo assays to determine the ability of the conjugate to selectively inhibit renal action and thereby control blood pressure. This in vivo experiment was conducted to characterize the effects of the Example 79 conjugate on spontaneously hypertensive rats (SHR) by acute administration i.v. and by chronic administration i.v. The Example 18 compound or saline vehicle was infused continuously for four days in SHR. Mean arterial pressure was measured (Gould Chart Recorder, model 3800; Statham P23Db pressure transducer) via an indwelling femoral artery catheter between 10:00a.m. and 2:00 P. M. each day. The Example 79 conjugate (10 mg/hr) or saline was infused via a jugular vein catheter with a Harvard infusion pump. After administration of the Example 79 conjugate, there was observed a lowered mean arterial pressure as compared to the saline vehicle control as reported in Table V and also in Fig. 1. A test was conducted to determine whether the Example 79 conjugate would antagonize non-renal, vascular angiotensin II receptors. In this test AII was administered by bolus injection (100 ng/kg) to the SHR rats (described above) on the control day and on days 1, 3 and 4 during conjugate infusion. No evidence for systemic angiotensin II receptor antagonism was observed, given the similar pressor responses to injections of angiotensin II on the control day and days 1, 3 and 4 of infusion of the Example 79 conjugate (see Figure 2). Tachycardia was observed on day 1 of the conjugate infusion, but heart rate was returned to control level during the next three days (see Figure 3).

TABLE V

Effect of Ex. #79 Conjugate on Mean
Arterial Pressure: Chronic Administration

Time (days):	Control	1	2	3	4
Ex. #18 Conjugate (10 mg/hr)					
MAP (mm Hg):	183	159	155	154	166
(SD)	±5	±7	±4	±6	±9

TABLE VI

Effect of Ex. #18 Conjugate on
AII Pressor Response

Time (days):	Control	1	3	4
		Ex. #18 Conjugate (10 mg/hr)		
	31	30	29	25
(SD)	±4	±6	±5	±3

TABLE VII

Effect of Ex. #79 Conjugate on Heart Rate

Time (days):	Control	1	2	3	4
Ex. #18 Conjugate (10 mg/hr)					
Beats/min.:	352	395	352	344	374
(SD)	±9	±21	±12	±22	±20

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more conjugates which comprises a first component selected from angiotensin II antagonist compounds of Formula I linked to a second component provided by an enzyme-cleavable moiety. Such pharmaceutical compositions further comprise one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The conjugates of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of a conjugate of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art. The conjugates and composition may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the conjugate. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of conjugate from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight, may be appropriate.

The conjugate may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose is from about 0.1 to 100 mg/kg body

weight injected per day in multiple doses depending on the disease being treated. A preferred daily dose would be from about 1 to 30 mg/kg body weight. Conjugates indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 100 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 100 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 50 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of active compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

The dosage regimen for treating a disease condition with the conjugates and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular conjugate employed, and thus may vary widely.

For therapeutic purposes, the conjugates of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the conjugate may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets

may contain a controlled-release formulation as may be provided in a dispersion of conjugate in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The conjugates may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

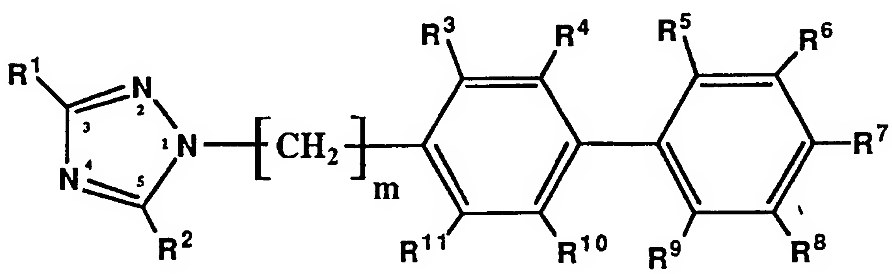
WHAT IS CLAIMED IS:

1. A conjugate comprising a residue of a biphenylalkyl 1H-substituted-1,2,4-triazole angiotensin II antagonist compound, said conjugate being renal selective.

2. Conjugate of Claim 1 comprising a first residue and a second residue, said first and second residues connected together by a cleavable bond, wherein said first residue is provided by said biphenylalkyl 1H-substituted-1,2,4-triazole angiotensin II antagonist compound, and wherein said second residue is capable of being cleaved from said first residue selectivity in the kidney.

3. Conjugate of Claim 2 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

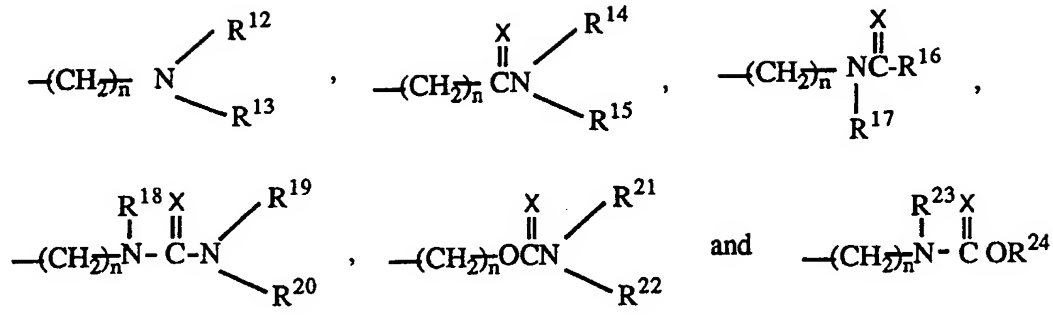
4. Conjugate of Claim 3 wherein said angiotensin II antagonist compound is selected from a class of compounds defined by Formula I:



(I)

wherein m is a number selected from one to four, inclusive;

wherein each of R^1 through R^{11} is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing groups has one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

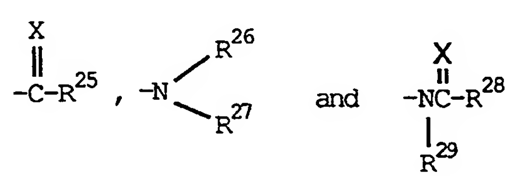
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{16} and R^{17} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

and wherein each of R^3 through R^{11} may be further independently selected from hydroxy and from acidic moieties of the formula

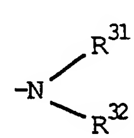
$-Y_nA$

wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

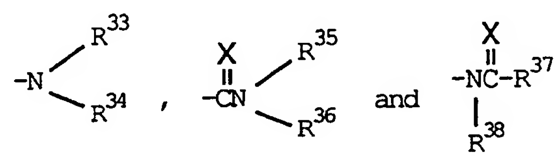
and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein each of R^{25}, R^{26}, R^{27}, R^{28} and R^{29} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, DR^{30} and



wherein D is selected from oxygen atom and sulfur atom and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

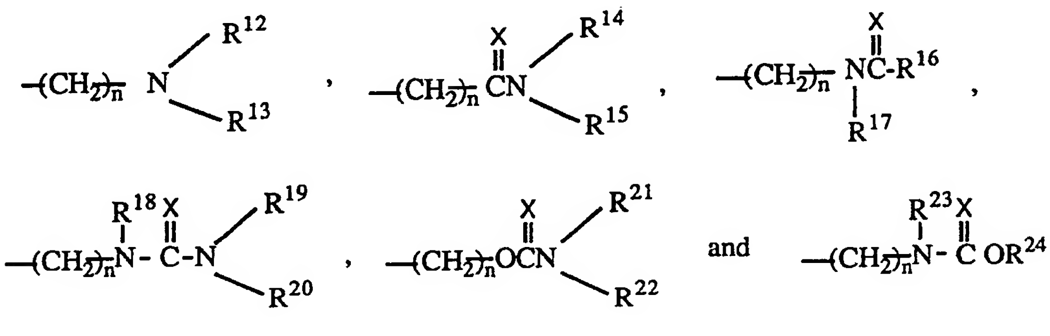
wherein each of R^{33}, R^{34}, R^{35}, R^{36}, R^{37} and R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein R^{26} and R^{27} taken together and R^{28} and R^{29} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{26} and R^{27} taken together and R^{31} and R^{32} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety.

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

5. Conjugate of Claim 4 wherein m is one; wherein each of R^1 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthio-carbonylthio, alkylthiothiocarbonyl, alkylthiothio-carbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur

and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

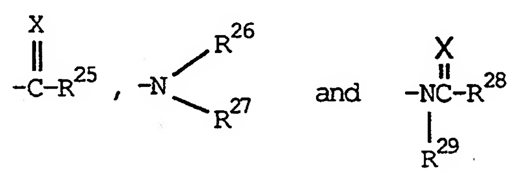
and wherein each of R^3 through R^{11} may be further independently selected from hydroxy and from acidic moieties of the formula

$$-Y_nA$$

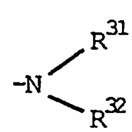
wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and

heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

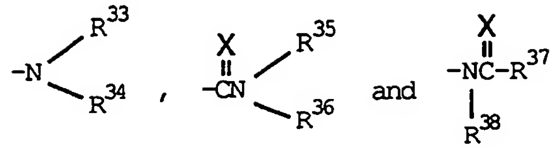
and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein each of R^{25}, R^{26}, R^{27}, R^{28} and R^{29} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

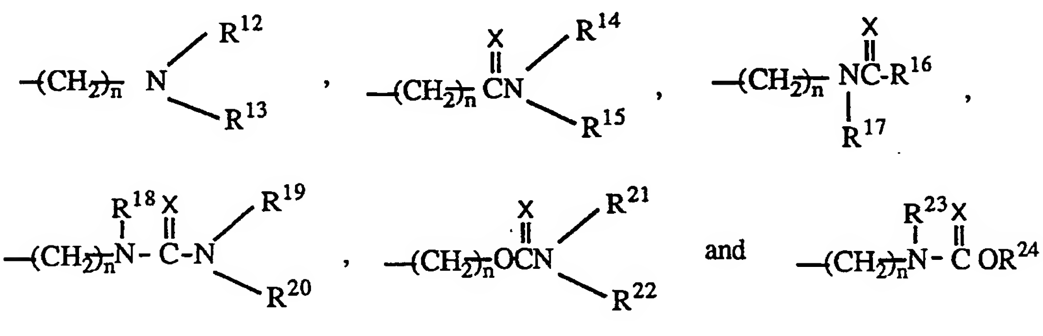
wherein each of R^{33} through R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

6. Conjugate of Claim 5 wherein m is one; wherein each of R^1 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalklylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms

selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

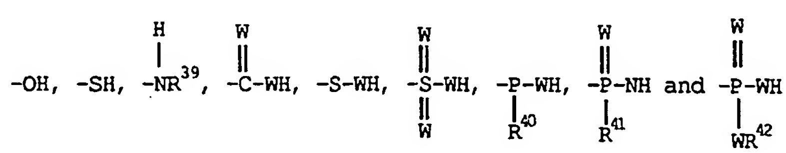
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be further independently selected from hydroxy and from acidic moieties of the formula

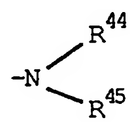
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive;

wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{40}, R^{41}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39}, R^{40}, R^{41} and R^{42} may be further independently selected from amino radical of the formula



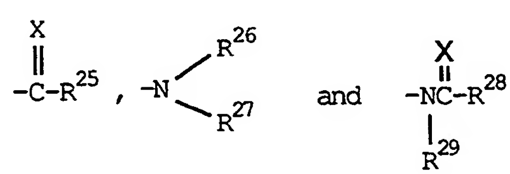
wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R^{44} and R^{45} may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or

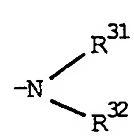
partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein each of R^{25}, R^{26}, R^{27}, R^{28} and R^{29} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR^{30} and



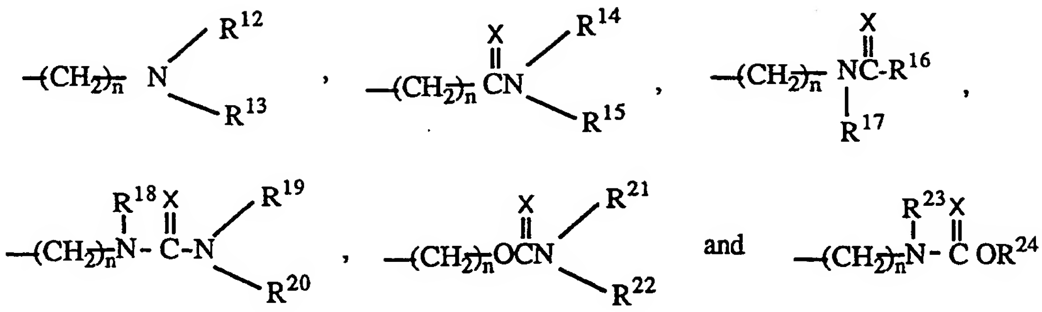
wherein D is selected from oxygen atom and sulfur atom, wherein R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl;

wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

7. Conjugate of Claim 6 wherein m is one; wherein each of R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

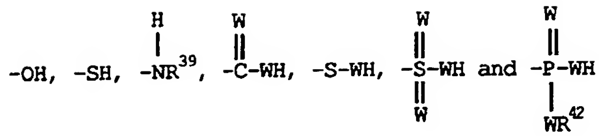
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

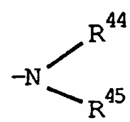
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which

heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

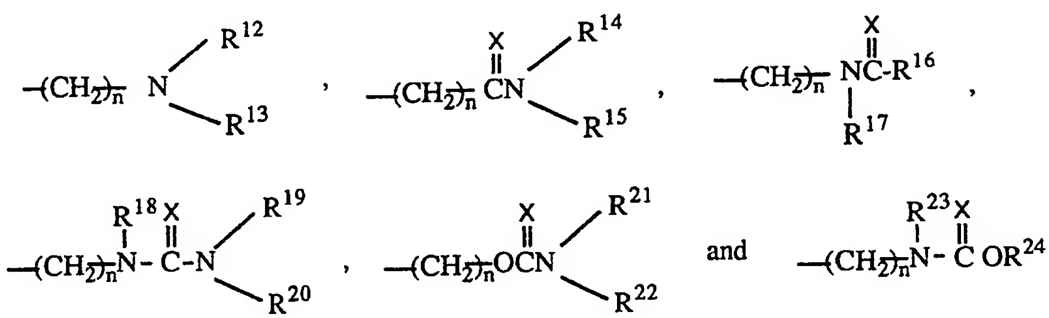
wherein each of R^1 through R^{11}, Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

8. Conjugate of Claim 7 wherein m is one; wherein each of R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido,

phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

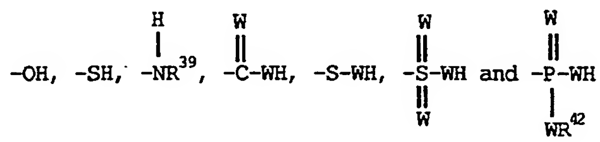
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio, mercapto and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

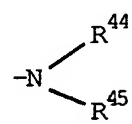
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

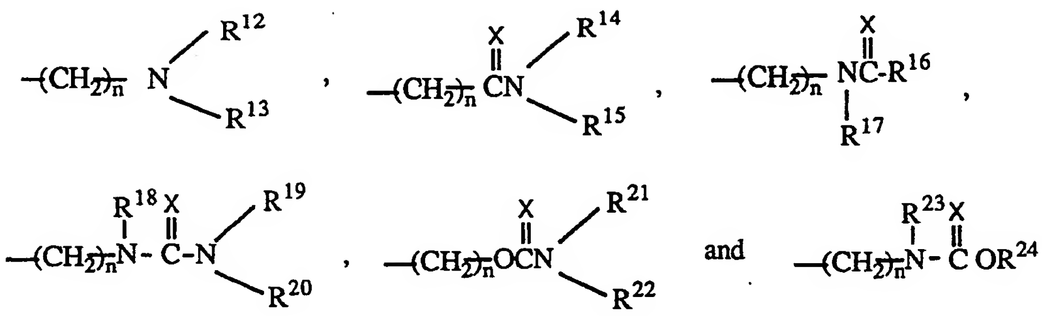
wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

wherein each of R^1 through R^{11}, Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

9. Conjugate of Claim 8 wherein m is one; wherein each of R^1 and R^2 is independently selected from alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole, tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula



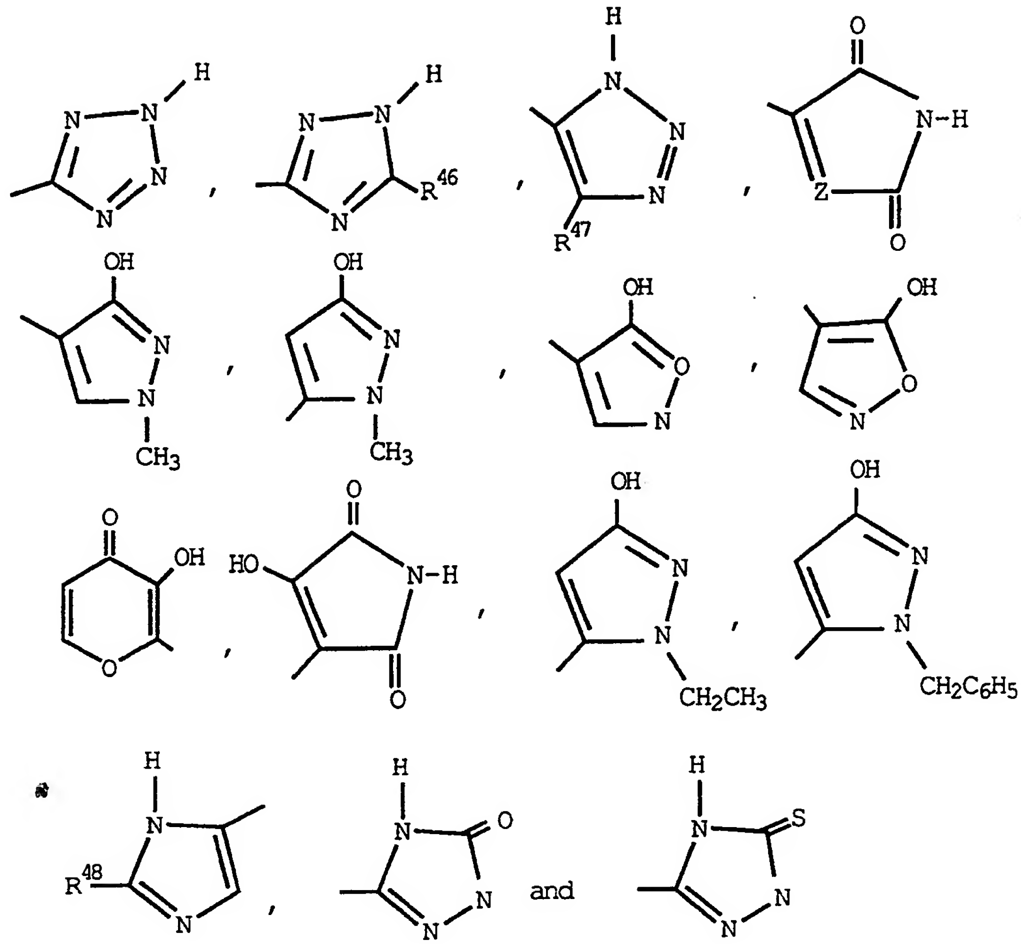
wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

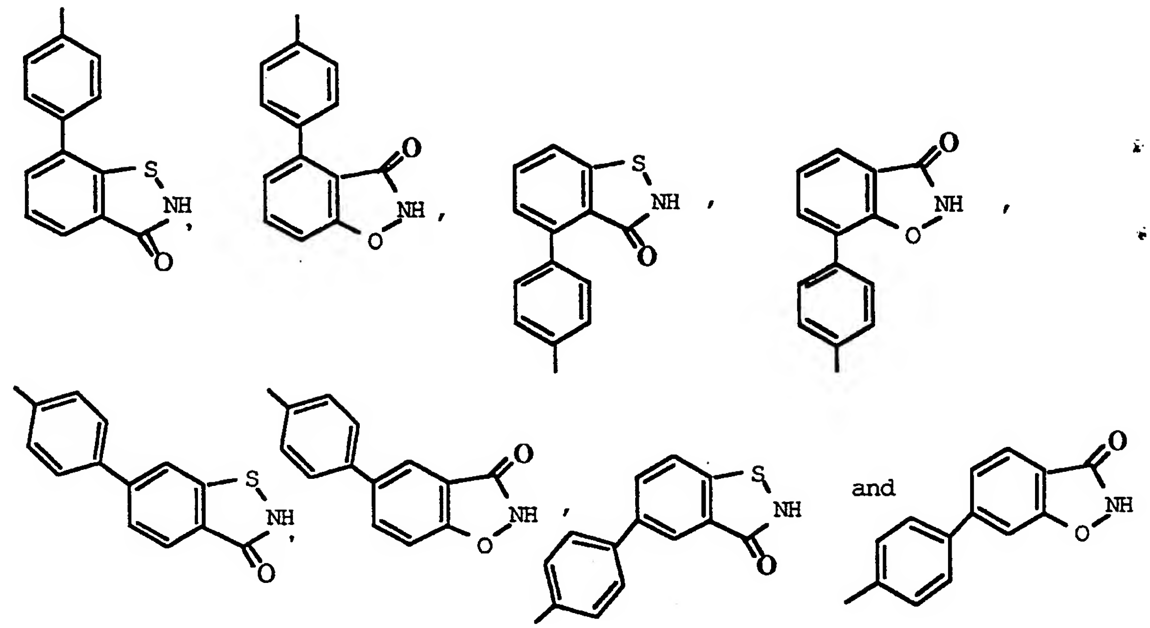
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties consisting of CO_2H, CO_2CH_3, SH, CH_2SH, C_2H_4SH, PO_3H_2, $NHSO_2CF_3$, $NHSO_2C_6F_5$, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, $CONHOCH_3$, $CONHOC_2H_5$, $CONHCF_3$, OH, CH_2OH, C_2H_4OH, OPO_3H_2, OSO_3H ,



wherein each of R^{46}, R^{47} and R^{48} is independently selected from H, Cl, CN, NO_2, CF_3, C_2F_5, C_3F_7, CHF_2, CH_2F, CO_2CH_3, $CO_2C_2H_5$, SO_2CH_3, SO_2CF_3 and $SO_2C_6F_5$; wherein Z is selected from O, S, NR^{49} and CH_2; wherein R^{49} is selected from hydrido, CH_3 and $CH_2C_6H_5$; and wherein said acidic moiety may be a heterocyclic acidic group attached at any two adjacent positions of R^3 through R^{11} so as to form a fused ring system so as to include one of the phenyl rings of the biphenyl moiety of Formula I, said biphenyl fused ring system selected from

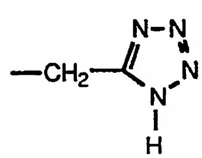


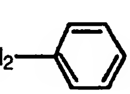
and the esters, amides and salts of said acidic moieties;

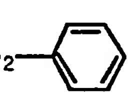
with the proviso that at least one of said R^1 through R^{24} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

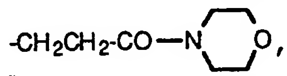
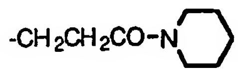
10. Conjugate of Claim 9 wherein m is one; wherein each of R^1 and R^2 is independently selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO,

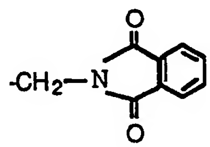
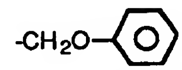
CH_2CO_2H, $CH(CH_3)CO_2H$, NO_2, Cl,  ,

$-CH_2OCOCH_2CH_2-$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$,

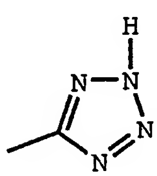
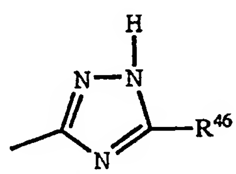
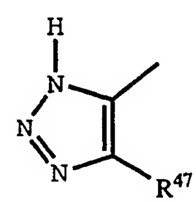
$-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl,

$-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H,

, , $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2OCSNHCH_3$, $-CH_2NHCSOC_3H_7$,

$-CH_2CH_2CH_2F$, $-CH_2ONO_2$, , $-CH_2SH$, ,

H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

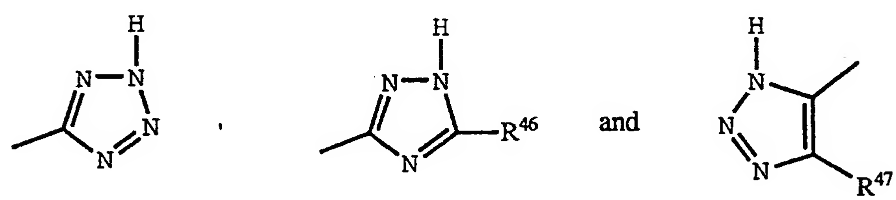
 ,  and 

wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

11. Conjugate of Claim 10 wherein m is one; wherein R^1 is selected from amino, aminomethyl, aminoethyl, aminopropyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein R^2 is selected from ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, 4-methylbutyl, tert-butyl, n-pentyl and neopentyl; wherein each of R^3, R^4, R^6, R^7, R^8, R^{10}, and R^{11} is hydrido; wherein one of R^5 and R^9 is hydrido and the other of R^5 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,



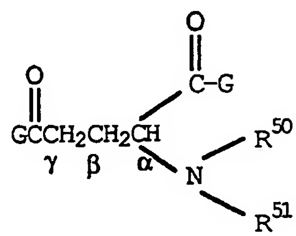
wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

12. Conjugate of Claim 3 wherein said second residue forms a kidney-enzyme-cleavable amide bond with the residue of said angiotensin II antagonist compound.

13. Conjugate of Claim 3 wherein said second residue is preferably selected from a class of compounds of Formula II:



(II)

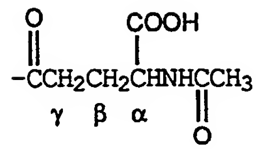
wherein each of R^{50} and R^{51} may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-OR^{52}$, $-SR^{53}$ and $>NR^{54}$ with each of R^{52}, R^{53} and R^{54} independently selected from alkyl; and wherein R^{54} may be further selected from hydrido; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

14. Conjugate of Claim 13 wherein each G substituent is hydroxy.

15. Conjugate of Claim 14 wherein each G substituent is hydroxy; wherein R^{50} is hydrido; and wherein R^{51} is selected from

$-\overset{\overset{\displaystyle O}{\|}}{C}R^{55}$ wherein R^{55} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

16. Conjugate of Claim 15 wherein said second residue is

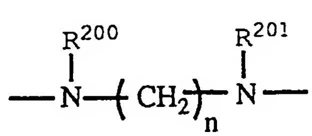


17. Conjugate of Claim 3 wherein said first residue is a biphenylalkyl 1H-substituted-1,2,4-triazole angiotensin II antagonist compound containing a terminal primary or secondary amino moiety selected from amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups selected from aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

18. Conjugate of Claim 3 wherein said first residue is provided by a biphenylalkyl 1H-substituted-1,2,4-triazole angiotensin II antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety.

19. Conjugate of Claim 18 wherein said moiety convertible to an amino terminal moiety is a carboxylic acid group reactable with an amino moiety of a diamino-terminated linker group to provide a terminal amino moiety which may then be further reacted with a carboxylic acid moiety of a compound providing said second residue so as to form a hydrolyzable amide bond.

20. Conjugate of Claim 19 wherein said diamino-terminated linker group is a divalent radical of Formula III:

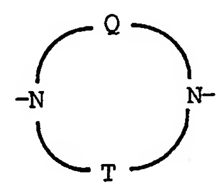


(III)

wherein each of R^{200} and R^{201} may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

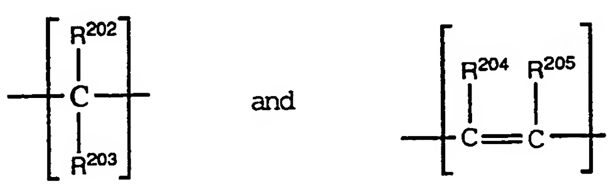
21. Conjugate of Claim 20 wherein each of R^{200} and R^{201} is hydrido.

22. Conjugate of Claim 19 wherein said diamino-terminated linker group is a divalent radical of Formula IV:



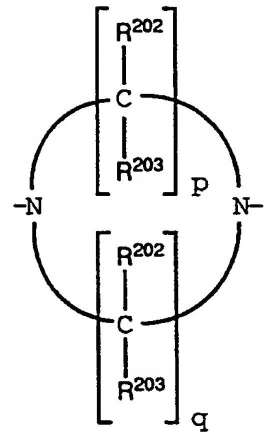
(IV)

wherein each of Q and T is one or more groups independently selected from



wherein each of R^{202} through R^{205} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

23. Conjugate of Claim 22 wherein said diamino-terminated linker group is a divalent radical of Formula V:



(V)

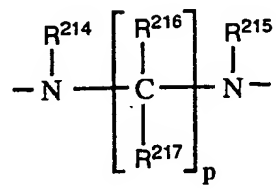
wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R^{202} and R^{203} is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R^{202} or R^{203} is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

24. Conjugate of Claim 23 wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.

25. Conjugate of Claim 24 wherein each of R^{202} and R^{203} is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three.

26. Conjugate of Claim 25 wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two.

27. Conjugate of Claim 19 wherein said diamino-terminated linker group is a divalent radical of Formula VI:



(VI)

wherein each of R^{214} through R^{217} is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

28. Conjugate of Claim 27 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three.

29. Conjugate of Claim 28 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido and alkyl; and wherein p is two.

30. Conjugate of Claim 29 wherein each of R^{214}, R^{215}, R^{216} and R^{217} is hydrido; and wherein p is two.

31. Conjugate of Claim 11 wherein said angiotensin II antagonist compound is selected from the group consisting of
methyl 4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylate;
4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid, hydrazide;
4'-[(5-butyl-3-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3-butyl-5-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-secbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-tertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(2-cyclohexylethyl))-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexanoyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-phenyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-phenylmethyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-benzoyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-butyl-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[3-butyl-5-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dipropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-disecbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-diisobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-ditertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dipentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-diisopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
5-[4'-[(5-butyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-butyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-butyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole; and
5-[4'-[[3-butyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

32. Conjugate of Claim 21 which is N-acetylglutamic acid, 5-[[4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]]carbonylhydrazide.

33. Conjugate of Claim 17 which is N^2-acetyl-N-[[5-butyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1,2,4-triazol-3-yl]methyl]-L-glutamine.

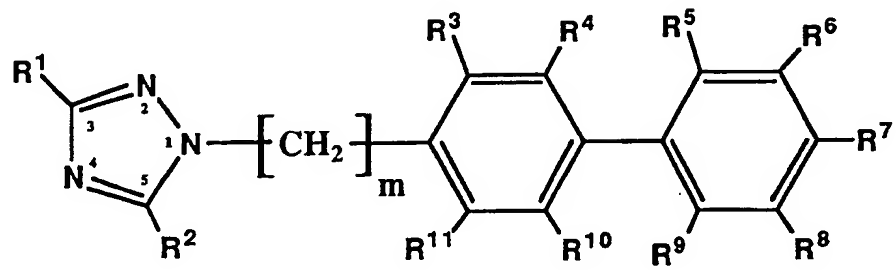
34. Conjugate of Claim 21 which is N-acetyl-L-glutamic acid, 5-[5-butyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1,2,4-traizol-3-yl]acetylhydrazide.

35. A pharmaceutical composition comprising one or more pharmaceutically-acceptable carriers or diluents and a therapeutically-effective amount of a renal-selective conjugate, said renal selective conjugate comprising a residue of a biphenylalkyl 1H-substituted-1,2,4-triazole angiotensin II antagonist compound.

36. The composition of Claim 35 comprising a first residue and a second residue, said first and second residues connected together by a cleavable bond, wherein said first residue is provided by said biphenylalkyl 1H-substituted-1,2,4-triazole angiotensin II antagonist compound, and wherein said second residue is capable of being cleaved from said first residue selectivity in the kidney.

37. The composition of Claim 36 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

38. The composition of Claim 37 wherein said angiotensin II antagonist compound is selected from a class of compounds defined by Formula I:

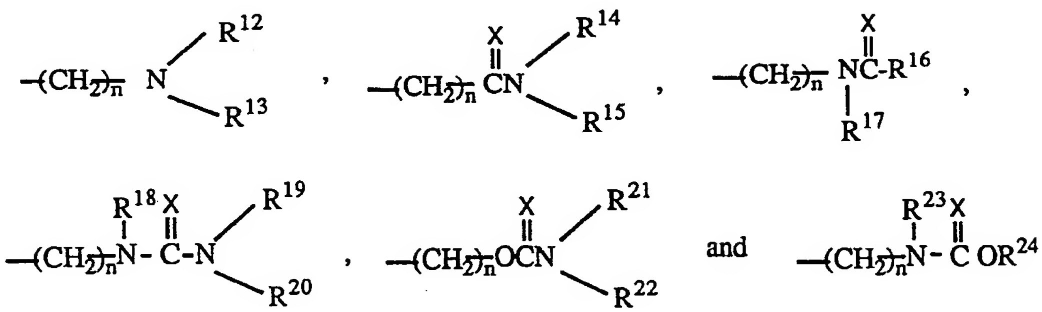


(I)

wherein m is a number selected from one to four, inclusive;

wherein each of R^1 through R^{11} is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing groups has one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through

R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

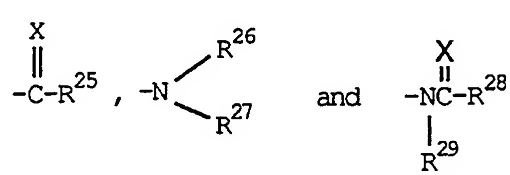
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{16} and R^{17} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

and wherein each of R^3 through R^{11} may be further independently selected from hydroxy and from acidic moieties of the formula

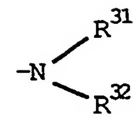
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

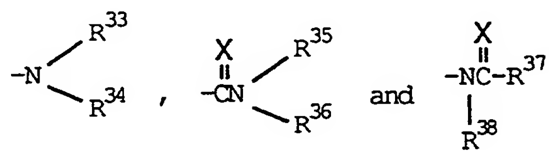
and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein each of R^{25}, R^{26}, R^{27}, R^{28} and R^{29} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, DR^{30} and



wherein D is selected from oxygen atom and sulfur atom and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each of R^{33}, R^{34}, R^{35}, R^{36}, R^{37} and R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein R^{26} and R^{27} taken together and R^{28} and R^{29} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{26} and R^{27} taken together and R^{31} and R^{32} taken together may each form an aromatic heterocyclic group having five ring members

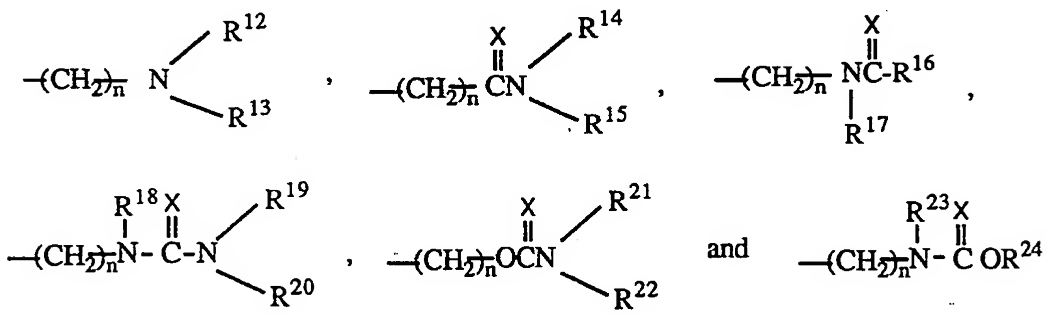
including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety.

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

39. The composition of Claim 38 wherein m is one; wherein each of R^1 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthio-carbonylthio, alkylthiothiocarbonyl, alkylthiothio-carbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and

cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

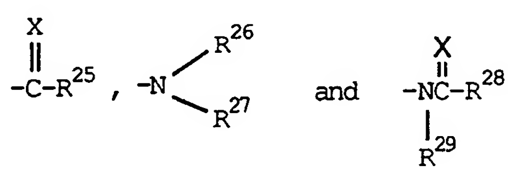
and wherein each of R^3 through R^{11} may be further independently selected from hydroxy and from acidic moieties of the formula

$$-Y_nA$$

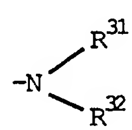
wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently

selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

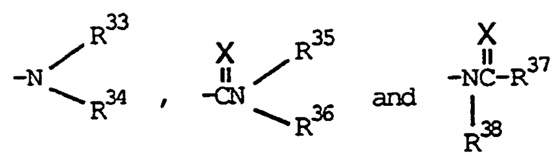
and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein each of R^{25}, R^{26}, R^{27}, R^{28} and R^{29} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

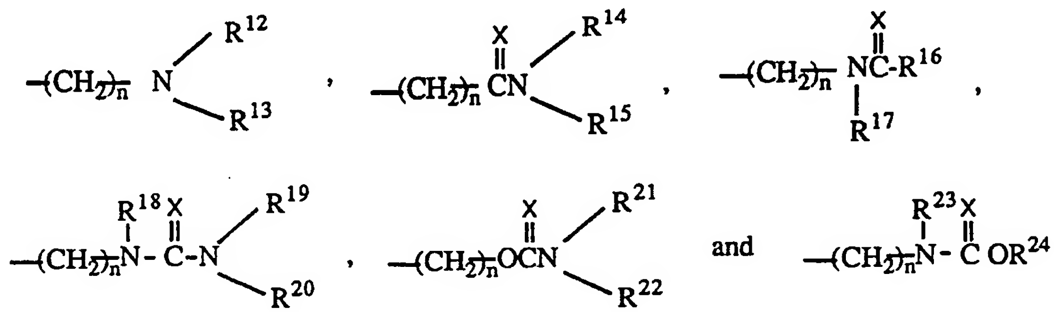
wherein each of R^{33} through R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

40. The composition of Claim 39 wherein m is one; wherein each of R^1 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalklylcarbonylalkyl wherein each of said

heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

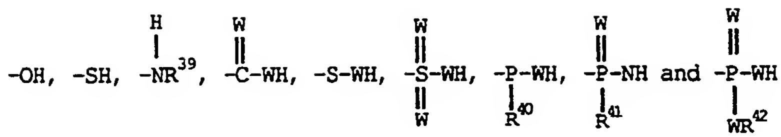
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be further independently selected from hydroxy and from acidic moieties of the formula

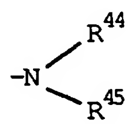
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive;

wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{40}, R^{41}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39}, R^{40}, R^{41} and R^{42} may be further independently selected from amino radical of the formula



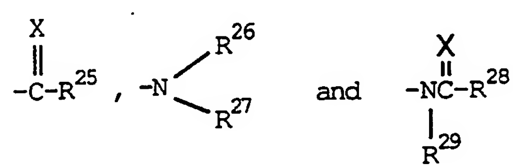
wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R^{44} and R^{45} may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members,

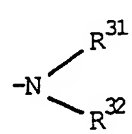
which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein each of R^{25}, R^{26}, R^{27}, R^{28} and R^{29} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, wherein R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl;

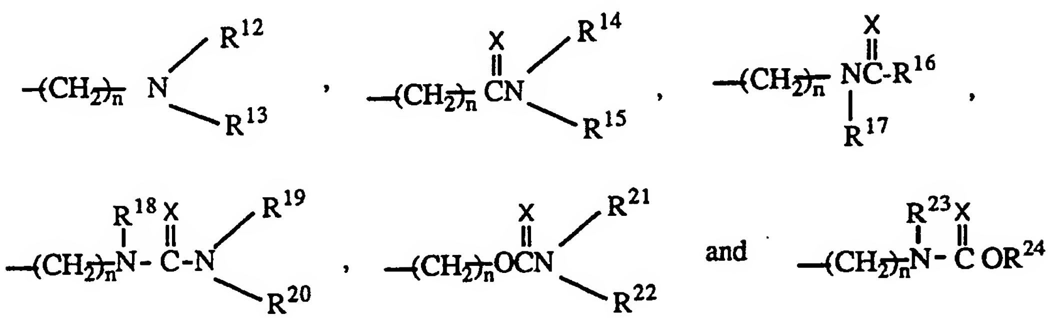
wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

41. The composition of Claim 40 wherein m is one; wherein each of R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be

further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

$$-OH,\ -SH,\ -\overset{\overset{\displaystyle H}{|}}{N}R^{39},\ -\overset{\overset{\displaystyle W}{\|}}{C}-WH,\ -S-WH,\ -\underset{\underset{\displaystyle W}{\|}}{\overset{\overset{\displaystyle W}{\|}}{S}}-WH \text{ and } -\underset{\underset{\displaystyle WR^{42}}{|}}{\overset{\overset{\displaystyle W}{\|}}{P}}-WH$$

wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula

$$-N\begin{matrix} \diagup R^{44} \\ \diagdown R^{45} \end{matrix}$$

wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one

hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

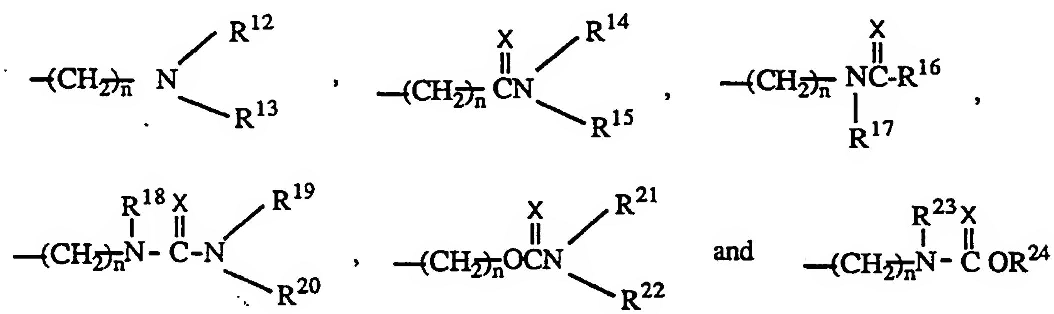
wherein each of R^1 through R^{11}, Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

42. The composition of Claim 41 wherein m is one; wherein each of R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl,

alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

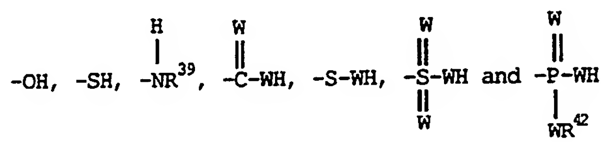
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio, mercapto and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

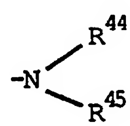
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of

the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

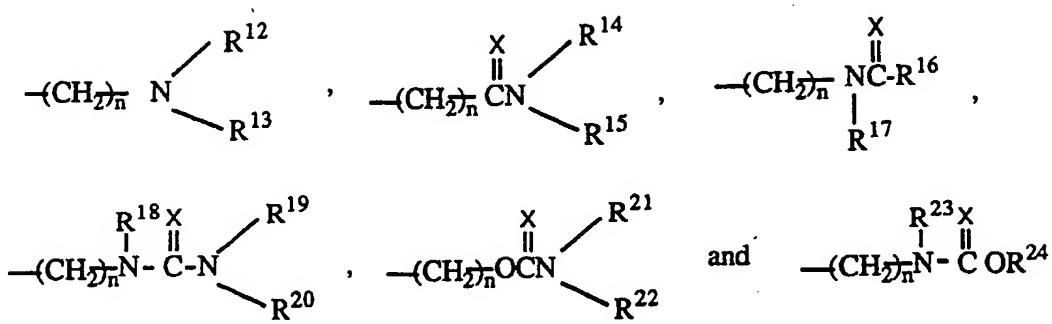
wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

wherein each of R^1 through R^{11}, Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

43. The composition of Claim 42 wherein m is one; wherein each of R^1 and R^2 is independently selected from alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole, tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula



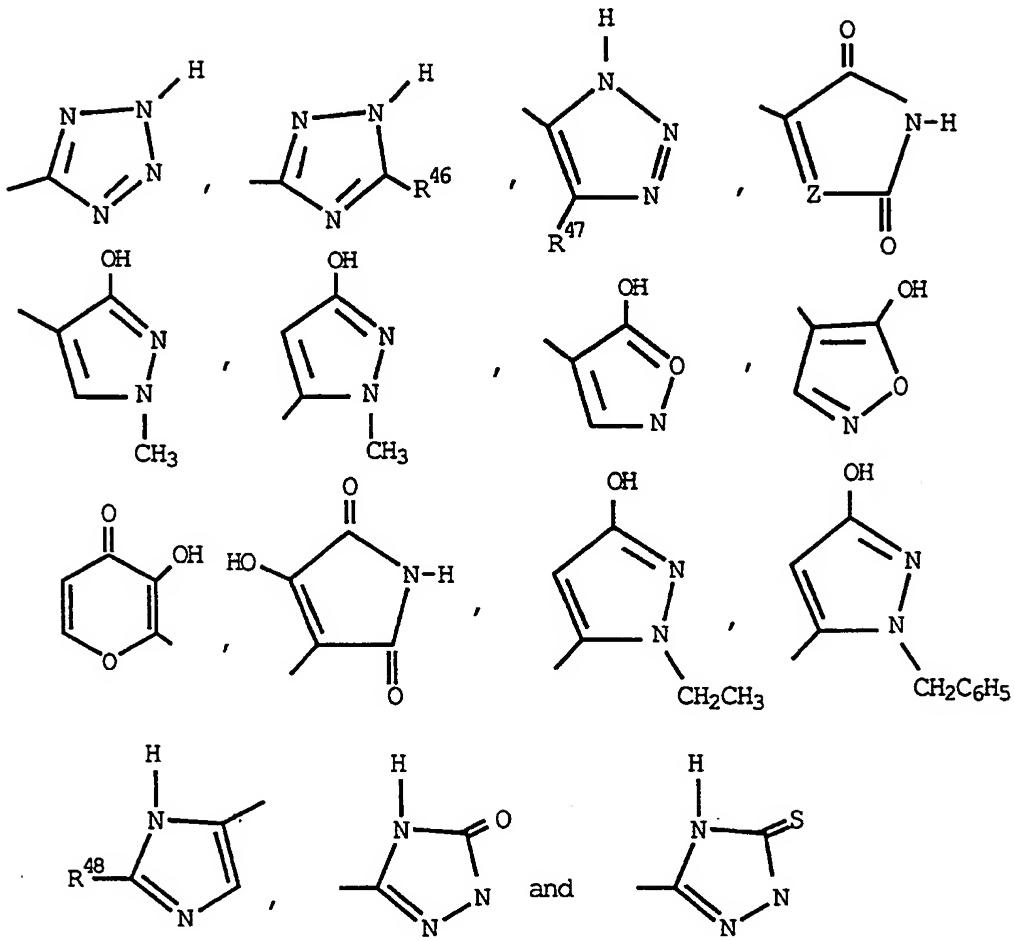
wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

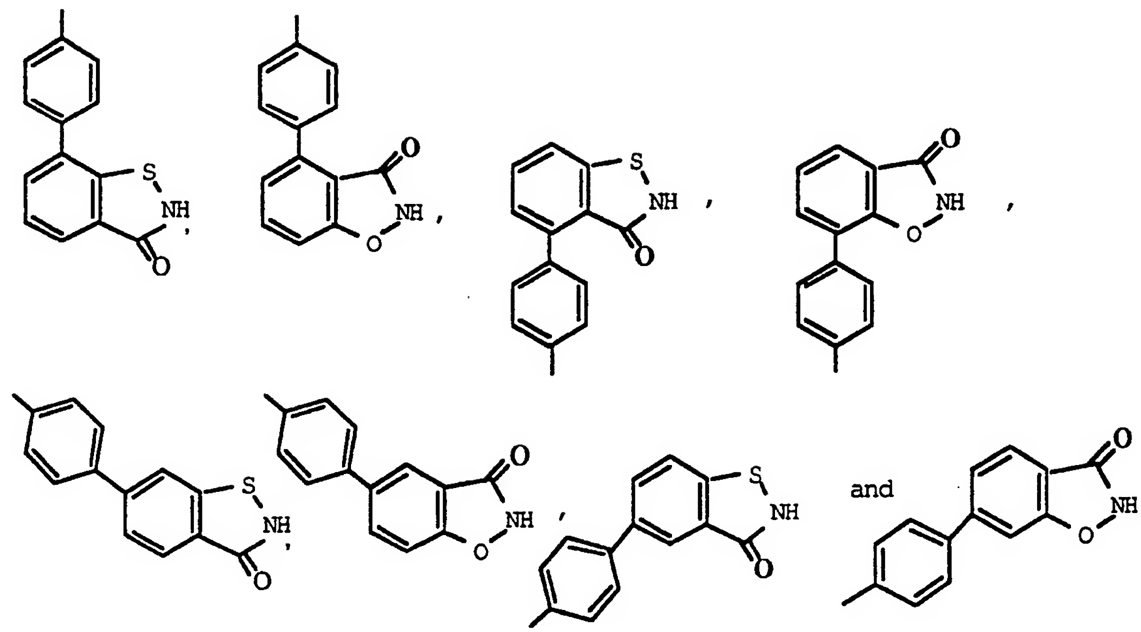
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties consisting of CO_2H, CO_2CH_3, SH, CH_2SH, C_2H_4SH, PO_3H_2, $NHSO_2CF_3$, $NHSO_2C_6F_5$, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, $CONHOCH_3$, $CONHOC_2H_5$, $CONHCF_3$, OH, CH_2OH, C_2H_4OH, OPO_3H_2, OSO_3H ,



wherein each of R^{46}, R^{47} and R^{48} is independently selected from H, Cl, CN, NO_2, CF_3, C_2F_5, C_3F_7, CHF_2, CH_2F, CO_2CH_3, $CO_2C_2H_5$, SO_2CH_3, SO_2CF_3 and $SO_2C_6F_5$; wherein Z is selected from O, S, NR^{49} and CH_2; wherein R^{49} is selected from hydrido, CH_3 and $CH_2C_6H_5$; and wherein said acidic moiety may be a heterocyclic acidic group attached at any two adjacent positions of R^3 through R^{11} so as to form a fused ring system so as to include one of the phenyl rings of the biphenyl moiety of Formula I, said biphenyl fused ring system selected from

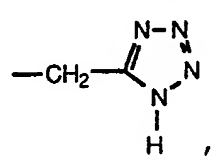


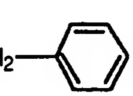
and the esters, amides and salts of said acidic moieties;

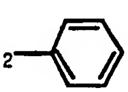
with the proviso that at least one of said R^1 through R^{24} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

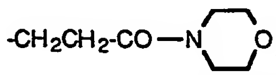
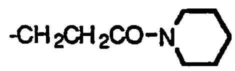
44. The composition of Claim 43 wherein m is one; wherein each of R^1 and R^2 is independently selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO,

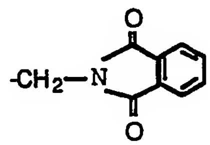
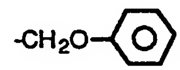
CH_2CO_2H, $CH(CH_3)CO_2H$, NO_2, Cl,  ,

$-CH_2OCOCH_2CH_2-$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$,

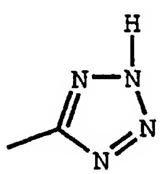
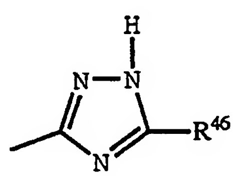
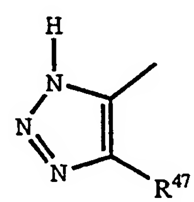
$-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl,

$-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H,

, , $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2OCSNHCH_3$, $-CH_2NHCSOC_3H_7$,

$-CH_2CH_2CH_2F$, $-CH_2ONO_2$, , $-CH_2SH$, ,

H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

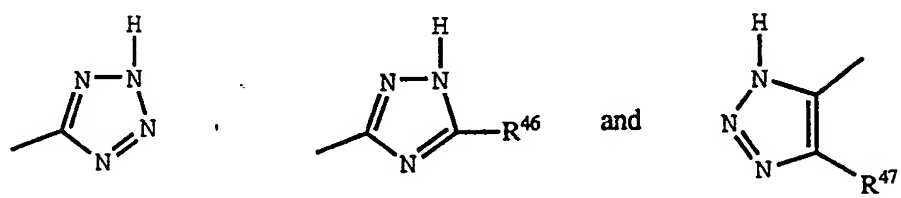
 ,  and 

wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

45. The composition of Claim 44 wherein m is one; wherein R^1 is selected from amino, aminomethyl, aminoethyl, aminopropyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein R^2 is selected from ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, 4-methylbutyl, tert-butyl, n-pentyl and neopentyl; wherein each of R^3, R^4, R^6, R^7, R^8, R^{10}, and R^{11} is hydrido; wherein one of R^5 and R^9 is hydrido and the other of R^5 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,



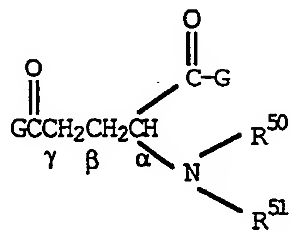
wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

46. The composition of Claim 37 wherein said second residue forms a kidney-enzyme-cleavable amide bond with the residue of said angiotensin II antagonist compound.

47. The composition of Claim 37 wherein said second residue is preferably selected from a class of compounds of Formula II:



(II)

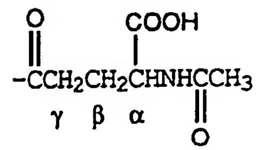
wherein each of R^{50} and R^{51} may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-OR^{52}$, $-SR^{53}$ and $>NR^{54}$ with each of R^{52}, R^{53} and R^{54} independently selected from alkyl; and wherein R^{54} may be further selected from hydrido; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

48. The composition of Claim 47 wherein each G substituent is hydroxy.

49. The composition of Claim 48 wherein each G substituent is hydroxy; wherein R^{50} is hydrido; and wherein R^{51} is selected from

$-\overset{\overset{O}{\|}}{C}R^{55}$ wherein R^{55} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

50. The composition of Claim 49 wherein said second residue is

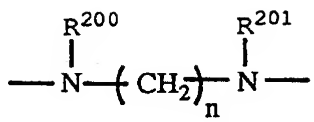


51. Conjugate of Claim 37 wherein said first residue is provided by a biphenylalkyl 1H-substituted-1,2,4-triazole angiotensin II antagonist compound containing a terminal primary or secondary amino moiety selected from amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups selected from aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

52. The composition of Claim 37 wherein said first residue is provided by a biphenylalkyl 1H-substituted-1,2,4-triazole angiotensin II antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety.

53. The composition of Claim 52 wherein said moiety convertible to an amino terminal moiety is a carboxylic acid group reactable with an amino moiety of a diamino-terminated linker group to provide a terminal amino moiety which may then be further reacted with a carboxylic acid moiety of a compound providing said second residue so as to form a hydrolyzable amide bond.

54. The composition of Claim 53 wherein said diamino-terminated linker group is a divalent radical of Formula III:

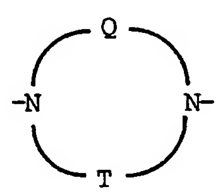


(III)

wherein each of R^{200} and R^{201} may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

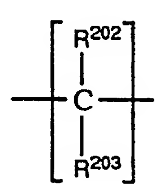
55. The composition of Claim 54 wherein each of R^{200} and R^{201} is hydrido.

56. The composition of Claim 53 wherein said diamino-terminated linker group is a divalent radical of Formula IV:

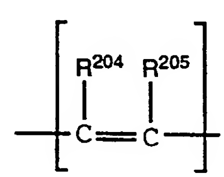


(IV)

wherein each of Q and T is one or more groups independently selected from



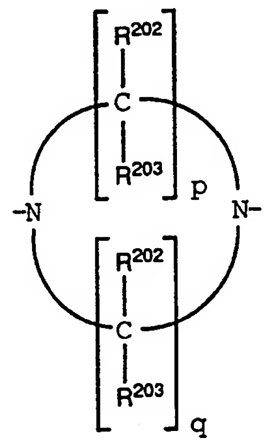
and



wherein each of R^{202} through R^{205} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino,

monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

57. The composition of Claim 56 wherein said diamino-terminated linker group is a divalent radical of Formula V:



(V)

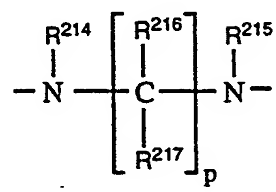
wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R^{202} and R^{203} is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R^{202} or R^{203} is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

58. The composition of Claim 57 wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.

59. The composition of Claim 58 wherein each of R^{202} and R^{203} is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three.

60. The composition of Claim 59 wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two.

61. The composition of Claim 53 wherein said diamino-terminated linker group is a divalent radical of Formula VI:



(VI)

wherein each of R^{214} through R^{217} is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

62. The composition of Claim 61 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three.

63. The composition of Claim 62 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido and alkyl; and wherein p is two.

64. The composition of Claim 63 wherein each of R^{214}, R^{215}, R^{216} and R^{217} is hydrido; and wherein p is two.

65. The composition of Claim 45 wherein said angiotensin II antagonist compound is selected from the group consisting of
methyl 4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylate;
4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid, hydrazide;
4'-[(5-butyl-3-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3-butyl-5-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-secbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-tertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(2-cyclohexylethyl))-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexanoyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-butyl-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-phenyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-phenylmethyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-benzoyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[3-butyl-5-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dipropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-disecbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(3,5-diisobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-ditertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dipentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-diisopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
5-[4'-[(5-butyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[[3-butyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole; and

5-[4'-[[3-butyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

66. The composition of Claim 55 wherein said angiotensin II antagonist compound is N-acetylglutamic acid, 5-[[4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]]carbonylhydrazide.

67. The composition of Claim 51 wherein said angiotensin II antagonist compound is N^2-acetyl-N-[[5-butyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1,2,4-triazol-3-yl]methyl]-L-glutamine.

68. The composition of Claim 55 wherein said angiotensin II antagonist compound is N-acetyl-L-glutamic acid, 5-[5-butyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1,2,4-traizol-3-yl]acetylhydrazide.

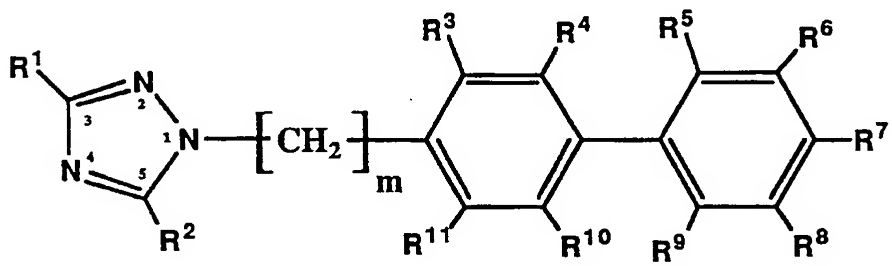
69. A method for treating a circulatory disorder, said method comprising administering to a patient afflicted with or susceptible to said disorder a therapeutically-effective amount of a renal-selective conjugate, said renal-selective conjugate comprising a residue of a biphenylalkyl 1H-substituted-1,2,4-triazole angiotensin II antagonist compound.

70. The method of Claim 69 comprising a first residue and a second residue, said first and second residues connected together by a cleavable bond, wherein said first residue is provided by said biphenylalkyl 1H-substituted-1,2,4-triazole angiotensin II antagonist compound, and wherein said second residue is capable of being cleaved from said first residue selectivity in the kidney.

71. The method of Claim 70 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and

second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

72. The method of Claim 71 wherein said angiotensin II antagonist compound is selected from a class of compounds defined by Formula I:

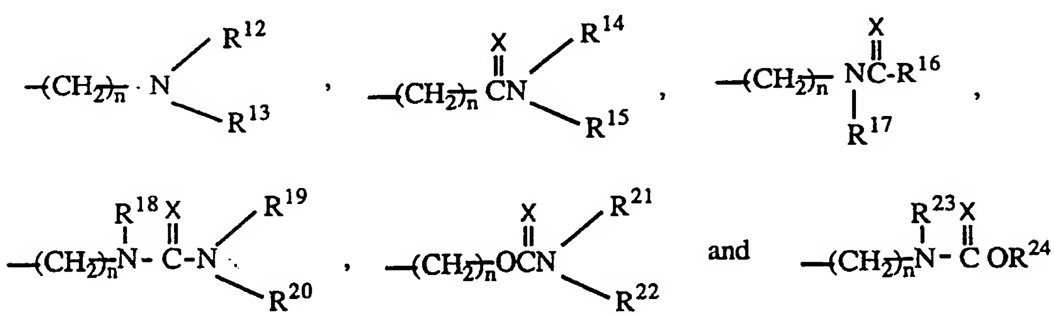


(I)

wherein m is a number selected from one to four, inclusive;

wherein each of R^1 through R^{11} is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl,

aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing groups has one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{16} and R^{17} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially

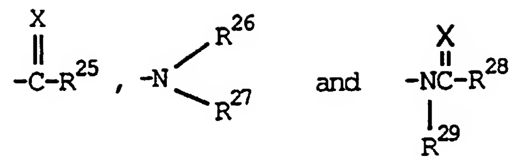
unsaturated; wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

and wherein each of R^3 through R^{11} may be further independently selected from hydroxy and from acidic moieties of the formula

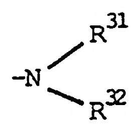
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

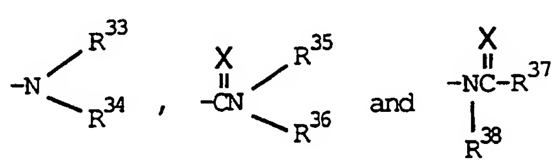
and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein each of R^{25}, R^{26}, R^{27}, R^{28} and R^{29} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, DR^{30} and



wherein D is selected from oxygen atom and sulfur atom and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each of R^{33}, R^{34}, R^{35}, R^{36}, R^{37} and R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein R^{26} and

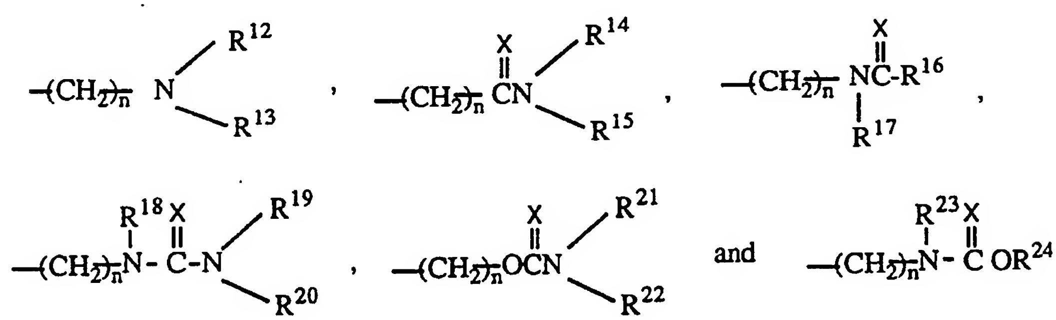
R^{27} taken together and R^{28} and R^{29} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{26} and R^{27} taken together and R^{31} and R^{32} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety.

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

73. The method of Claim 72 wherein m is one; wherein each of R^1 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthio-carbonylthio, alkylthiothiocarbonyl, alkylthiothio-carbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio,

arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

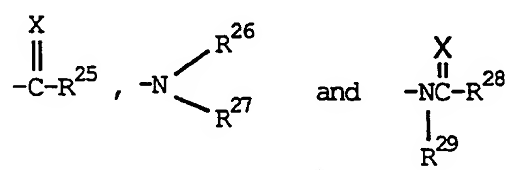
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be further independently selected from hydroxy and from acidic moieties of the formula

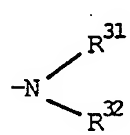
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula

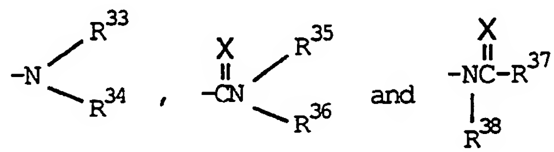


wherein X is selected from oxygen atom and sulfur atom; wherein each of R^{25}, R^{26}, R^{27}, R^{28} and R^{29} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, and R^{30} is selected from hydrido, alkyl, cycloalkyl,

cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

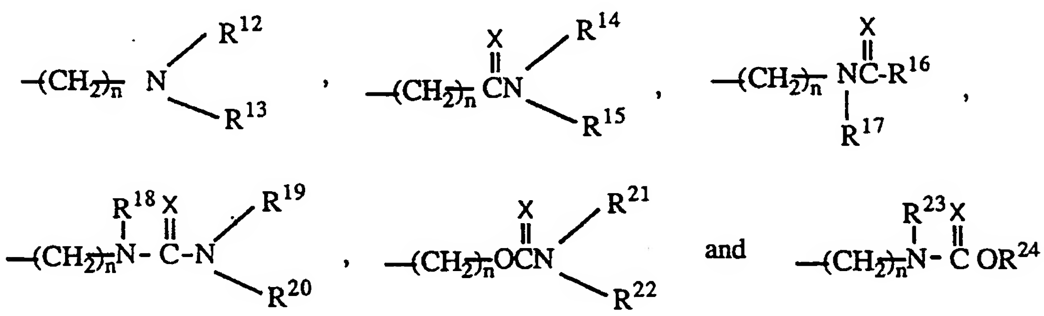
wherein each of R^{33} through R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

74. The method of Claim 73 wherein m is one; wherein each of R^1 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy,

alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalklylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

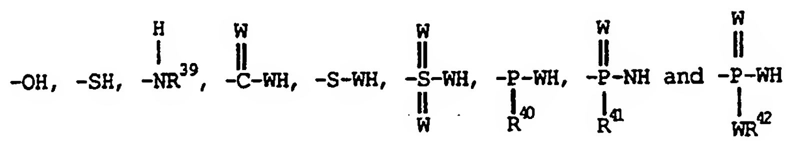
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be further independently selected from hydroxy and from acidic moieties of the formula

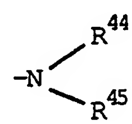
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive;

wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{40}, R^{41}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39}, R^{40}, R^{41} and R^{42} may be further independently selected from amino radical of the formula



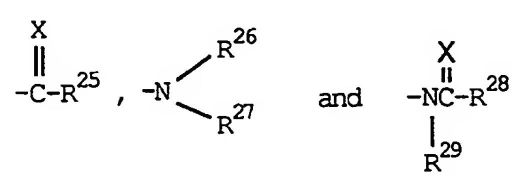
wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R^{44} and R^{45} may be further independently selected from hydroxy, alkoxy,

alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

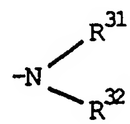
wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein each of R^{25}, R^{26}, R^{27}, R^{28} and R^{29} is selected from

hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, wherein R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl;

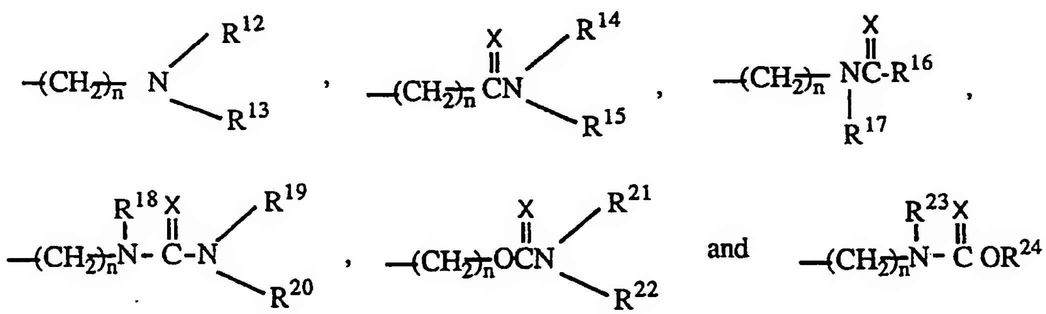
wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

75. The method of Claim 74 wherein m is one; wherein each of R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl,

heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

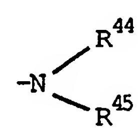
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

$$-OH,\ -SH,\ -\overset{\overset{\displaystyle H}{|}}{N}R^{39},\ -\overset{\overset{\displaystyle W}{\|}}{C}-WH,\ -S-WH,\ -\underset{\underset{\displaystyle W}{\|}}{\overset{\overset{\displaystyle W}{\|}}{S}}-WH \text{ and } -\underset{\underset{\displaystyle WR^{42}}{|}}{\overset{\overset{\displaystyle W}{\|}}{P}}-WH$$

wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen

and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

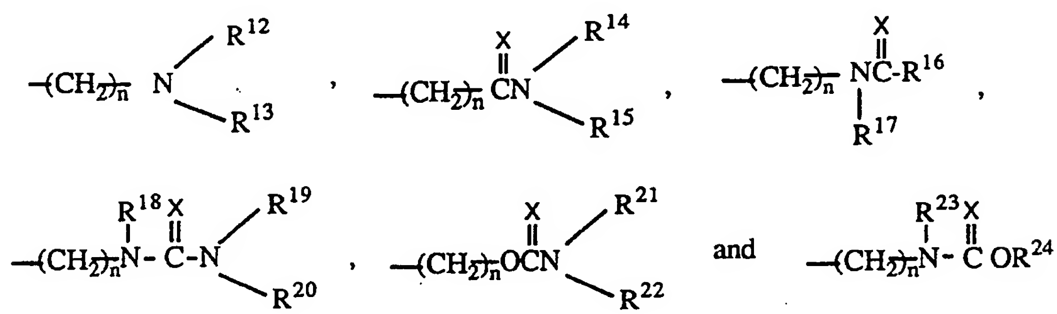
wherein each of R^1 through R^{11}, Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

76. The method of Claim 75 wherein m is one; wherein each of R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl,

cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^1 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

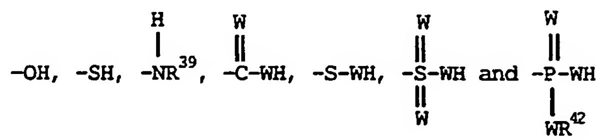
wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl,

alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio, mercapto and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

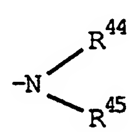
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring

may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

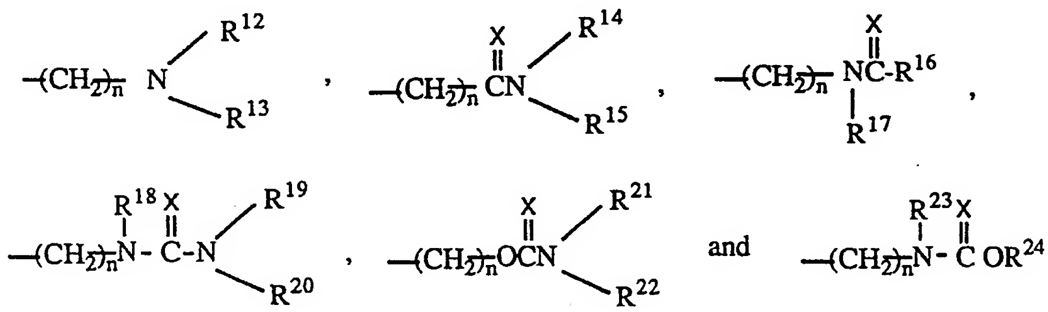
wherein each of R^1 through R^{11}, Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

77. The method of Claim 76 wherein m is one; wherein each of R^1 and R^2 is independently selected from alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phehylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercaptocarbonyl, alkoxycarbonyloxy,

alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole, tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula



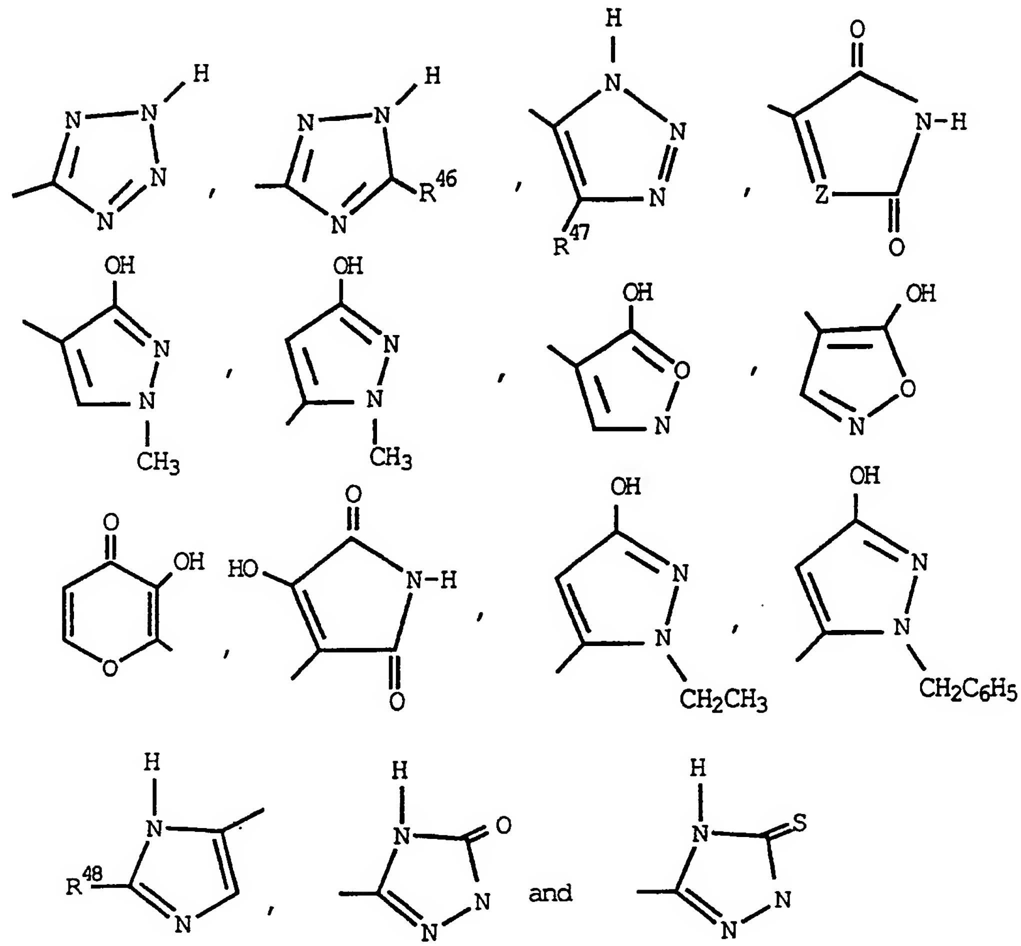
wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

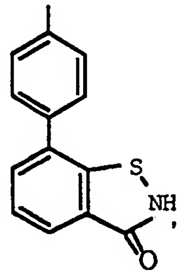
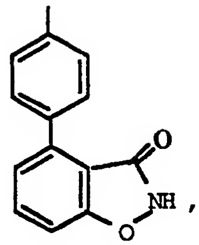
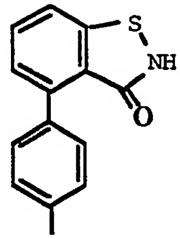
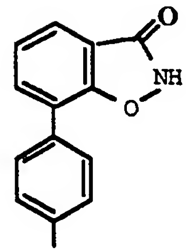
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

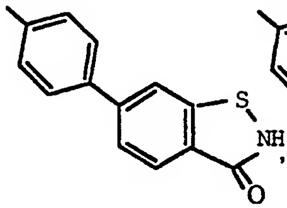
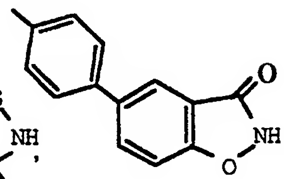
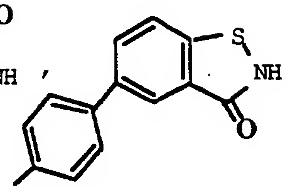
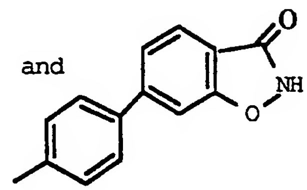
wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties consisting of CO_2H, CO_2CH_3, SH, CH_2SH, C_2H_4SH, PO_3H_2, $NHSO_2CF_3$, $NHSO_2C_6F_5$, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, $CONHOCH_3$, $CONHOC_2H_5$, $CONHCF_3$, OH, CH_2OH, C_2H_4OH, OPO_3H_2, OSO_3H ,



wherein each of R^{46}, R^{47} and R^{48} is independently selected from H, Cl, CN, NO_2, CF_3, C_2F_5, C_3F_7, CHF_2, CH_2F, CO_2CH_3, $CO_2C_2H_5$, SO_2CH_3, SO_2CF_3 and $SO_2C_6F_5$; wherein Z is selected from O, S, NR^{49} and CH_2; wherein R^{49} is selected from hydrido, CH_3 and $CH_2C_6H_5$; and wherein said acidic moiety may be a heterocyclic acidic group attached at any two adjacent positions of R^3 through R^{11} so as to form a fused ring system so as to include one of the phenyl rings of the biphenyl moiety of Formula I, said biphenyl fused ring system selected from

 ,  ,  ,  ,

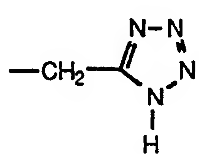
 ,  ,  and 

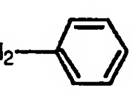
and the esters, amides and salts of said acidic moieties;

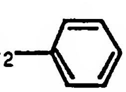
with the proviso that at least one of said R^1 through R^{24} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

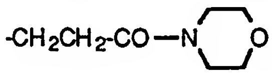
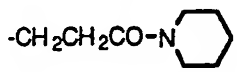
78. The method of Claim 77 wherein m is one; wherein each of R^1 and R^2 is independently selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO,

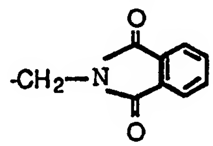
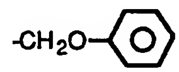
CH_2CO_2H, $CH(CH_3)CO_2H$, NO_2, Cl,  ,

$-CH_2OCOCH_2CH_2-$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$,

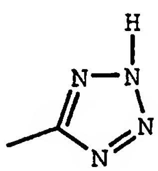
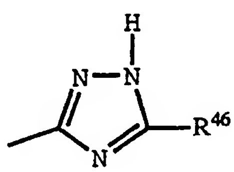
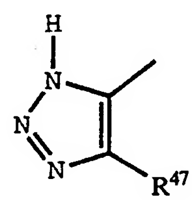
$-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl,

$-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H,

, , $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2OCSNHCH_3$, $-CH_2NHCSOC_3H_7$,

$-CH_2CH_2CH_2F$, $-CH_2ONO_2$, , $-CH_2SH$, ,

H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

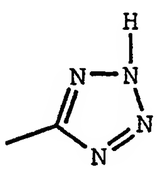
 ,  and 

wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

79. The method of Claim 78 wherein m is one; wherein R^1 is selected from amino, aminomethyl, aminoethyl, aminopropyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein R^2 is selected from ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, 4-methylbutyl, tert-butyl, n-pentyl and neopentyl; wherein each of R^3, R^4, R^6, R^7, R^8, R^{10}, and R^{11} is hydrido; wherein one of R^5 and R^9 is hydrido and the other of R^5 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,



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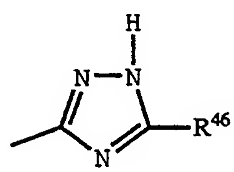
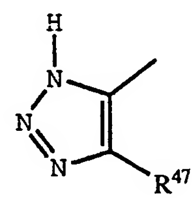


and


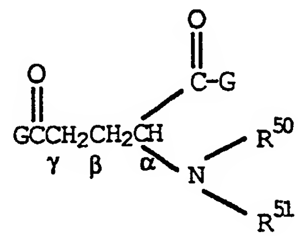
wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

80. The method of Claim 71 wherein said second residue forms a kidney-enzyme-cleavable amide bond with the residue of said angiotensin II antagonist compound.

81. The method of Claim 71 wherein said second residue is preferably selected from a class of compounds of Formula II:



(II)

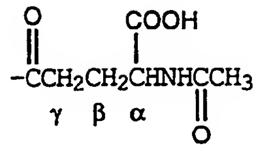
wherein each of R^{50} and R^{51} may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-OR^{52}$, $-SR^{53}$ and $>NR^{54}$ with each of R^{52}, R^{53} and R^{54} is independently selected from hydrido and alkyl; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

82. The method of Claim 81 wherein each G substituent is hydroxy.

83. The method of Claim 82 wherein each G substituent is hydroxy; wherein R^{50} is hydrido; and wherein R^{51} is selected from

$-\overset{O}{\overset{\|}{C}}R^{55}$ wherein R^{55} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

84. The method of Claim 83 wherein said second residue is

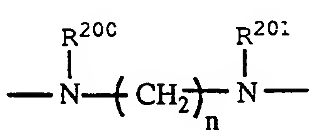


85. The method of Claim 71 wherein said first residue is a biphenylalkyl 1H-substituted-1,2,4-triazole angiotensin II antagonist compound containing a terminal primary or secondary amino moiety selected from amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups selected from aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

86. The method of Claim 71 wherein said first residue is provided by a biphenylalkyl 1H-substituted-1,2,4-triazole angiotensin II antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety.

87. The method of Claim 86 wherein said moiety convertible to an amino terminal moiety is a carboxylic acid group reactable with an amino moiety of a diamino-terminated linker group to provide a terminal amino moiety which may then be further reacted with a carboxylic acid moiety of a compound providing said second residue so as to form a hydrolyzable amide bond.

88. The method of Claim 87 wherein said diamino-terminated linker group is a divalent radical of Formula III:

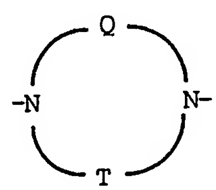


(III)

wherein each of R^{200} and R^{201} may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

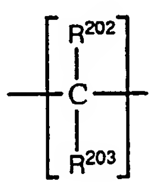
89. The method of Claim 88 wherein each of R^{200} and R^{201} is hydrido.

90. The method of Claim 87 wherein said diamino-terminated linker group is a divalent radical of Formula IV:

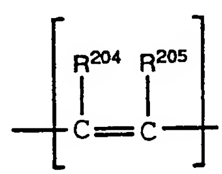


(IV)

wherein each of Q and T is one or more groups independently selected from

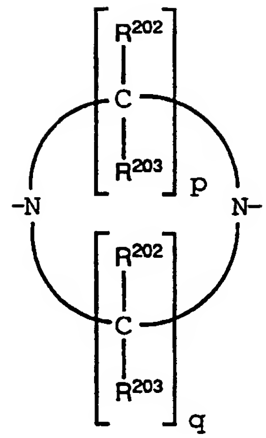


and



wherein each of R^{202} through R^{205} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

91. The method of Claim 90 wherein said diamino-terminated linker group is a divalent radical of Formula V:



(V)

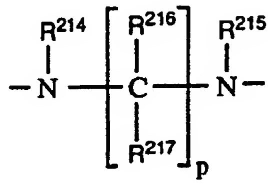
wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R^{202} and R^{203} is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R^{202} or R^{203} is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

92. The method of Claim 91 wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.

93. The method of Claim 92 wherein each of R^{202} and R^{203} is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three.

94. The method of Claim 93 wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two.

95. The method of Claim 87 wherein said diamino-terminated linker group is a divalent radical of Formula VI:



(VI)

wherein each of R^{214} through R^{217} is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

96. The method of Claim 95 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three.

97. The method of Claim 96 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido and alkyl; and wherein p is two.

98. The method of Claim 97 wherein each of R^{214}, R^{215}, R^{216} and R^{217} is hydrido; and wherein p is two.

99. The method of Claim 79 wherein said angiotensin II antagonist compound is selected from the group consisting of
methyl 4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylate;
4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid, hydrazide;
4'-[(5-butyl-3-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3-butyl-5-chloro-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-propyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-secbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-tertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-pentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-isopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexylmethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(2-cyclohexylethyl))-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-cyclohexanoyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxo-2-cyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-phenyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-phenylmethyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(5-butyl-3-benzoyl-1,2,4,-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[[5-butyl-3-(1-oxo-2-phenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-dimethoxypropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-dimethoxybutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxopropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1-oxopentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoroethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoropropyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[3-butyl-5-(1,1-difluorobutyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[[5-butyl-3-(1,1-difluoropentyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dipropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-isopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-disecbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-diisobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-ditertbutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-dipentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
4'-[(3,5-diisopentyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-carboxylic acid;
5-[4'-[(5-butyl-3-amino-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-butyl-3-aminomethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminoethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminopropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-aminobutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminophenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminoethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminocyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminomethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-aminoethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxy-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxymethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxyethyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;

5-[4'-[(5-butyl-3-carboxypropyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[(5-butyl-3-carboxybutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyphenylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylphenylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxyethylphenyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxycyclohexylethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylcyclohexylmethyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole;
5-[4'-[[3-butyl-5-(4-carboxymethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole; and
5-[4'-[[3-butyl-5-(4-carboxyethylcyclohexyl)-1H-1,2,4-triazol-1-yl]methyl][1,1'-biphenyl]-2-yl]-1H-tetrazole.

100. The method of Claim 89 wherein said renal-selective conjugate is N-acetylglutamic acid, 5-[[4'-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl][1,1'-biphenyl]-2-yl]]carbonylhydrazide.

101. The method of Claim 85 wherein said renal-selective conjugate is N^2-acetyl-N-[[5-butyl-1-[[2'-(1H-

tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1,2,4-triazol-3-yl]methyl]-L-glutamine.

102. The method of Claim 89 wherein said renal-selective conjugate is N-acetyl-L-glutamic acid, 5-[5-butyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1,2,4-traizol-3-yl]acetylhydrazide.

103. The method of Claim 69 wherein said circulatory disorder is a hypertensive-related disorder.

104. The method of Claim 103 wherein said hypertensive-related disorder is chronic hypertension.

105. The method of Claim 69 wherein said circulatory disorder is a sodium-retaining disorder.

106. The method of Claim 105 wherein said sodium-retaining disorder is congestive heart failure.

107. The method of Claim 105 wherein said sodium-retaining disorder is cirrhosis.

108. The method of Claim 105 wherein said sodium-retaining disorder is nephrosis.

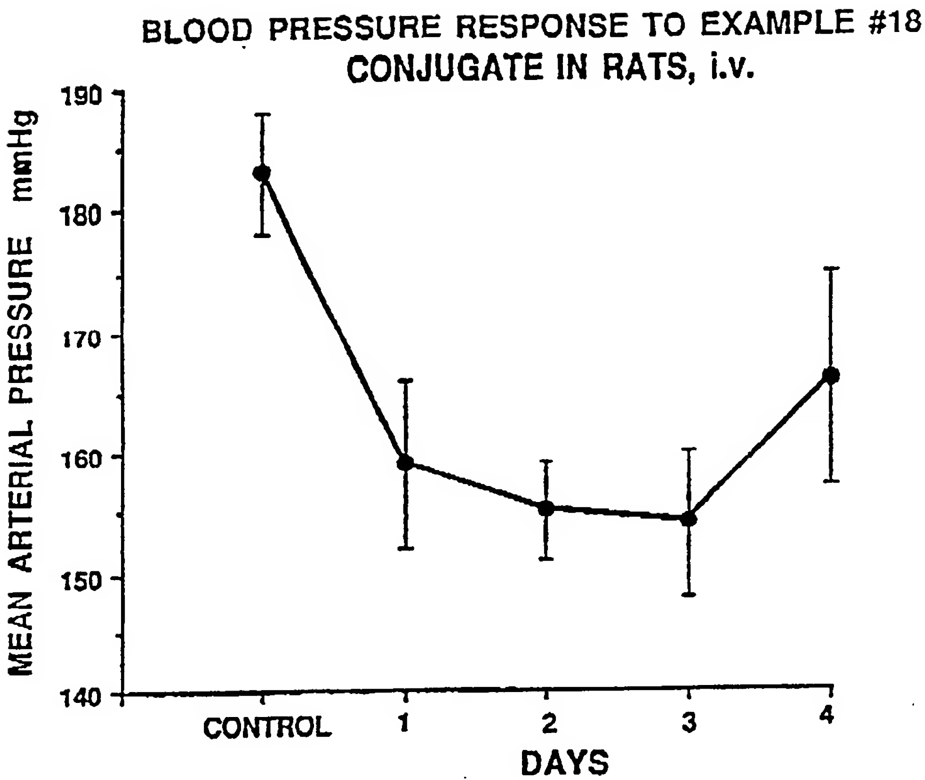

BLOOD PRESSURE RESPONSE TO EXAMPLE #18
CONJUGATE IN RATS, i.v.
MEAN ARTERIAL PRESSURE mmHg
190
180
170
160
150
140
CONTROL
1
2
3
4
DAYS

FIG. 1

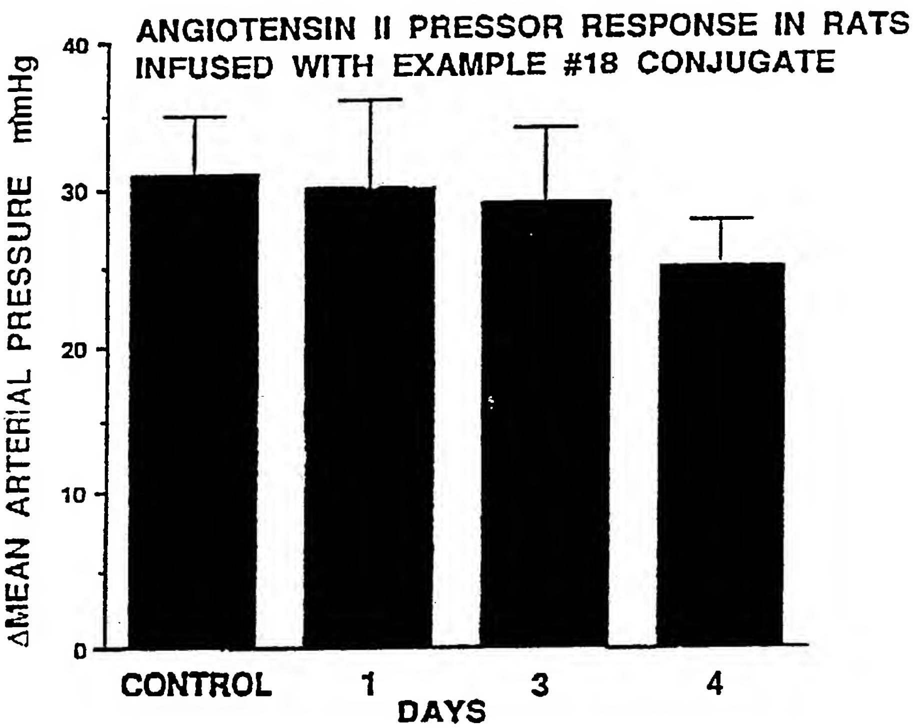

ANGIOTENSIN II PRESSOR RESPONSE IN RATS
INFUSED WITH EXAMPLE #18 CONJUGATE
ΔMEAN ARTERIAL PRESSURE mmHg
40
30
20
10
0
CONTROL
1
3
4
DAYS

FIG. 2

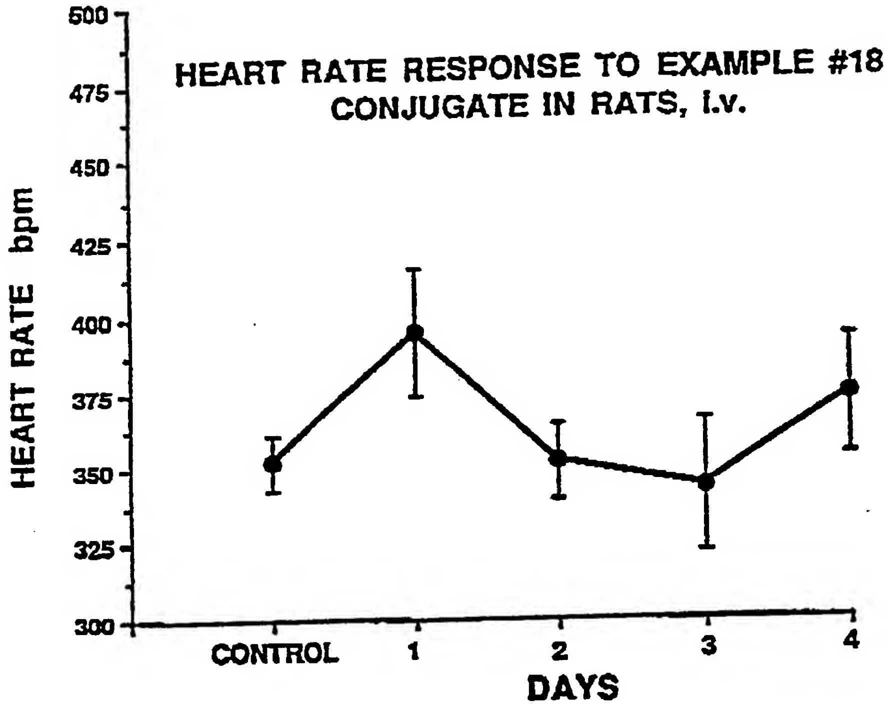

HEART RATE RESPONSE TO EXAMPLE #18
CONJUGATE IN RATS, i.v.
HEART RATE bpm
500
475
450
425
400
375
350
325
300
CONTROL
1
2
3
4
DAYS

FIG. 3

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